The Potential Impact of Stem Cell Therapy on our Industry

20th March 2013

Preamble
What the papers say

THE TIMES
Stem-cell treatments help ease patients’ blindness
First windpipe transplant on a child is declared a success

The Telegraph
Teenager injected with own stem cells in groundbreaking immune treatment
Scarred hearts can be restored to health with stem cell treatment, say researchers
Spinal cord injury treatment hope after new stem cell breakthrough

The Guardian
Neural stem cells injected into the brain of a zebrafish patient in world first
Tests begin on stem cell cure for rare heart disease

The potential of stem cell research is almost biblical in its scale, The Guardian, February 2009
Preamble
Cross-Industry Working Group

Aim
Develop an evidence-based value proposition of the potential impact of regenerative medicines on the protection and pensions industries.

Premise
1. Anticipated benefits of regenerative medicines are aligned with re/insurance products;
2. Hurdles limiting regenerative medicine development and market uptake represent an opportunity cost.
Agenda for today

• The scientist’s perspective  
  Dr Cathy Prescott
  – Science of stem cell therapy
  – Cell therapy products and pipeline
  – Challenges facing the stem cell Industry
  – Introduction to diabetes case study

• The economic and insurance perspective  
  John Woodford
  – The scale of the burden of ill health and the benefits of regenerative medicines
  – Costs and benefits within the health system and the wider economy
  – Case study: diabetes, the silent epidemic
  – Multi-state modelling and the challenges we face

The scientist’s perspective

Dr Catherine Prescott
What is a stem cell?

Stem Cell

Differentiation

'Shifted'

Progenitor Cell

Mature Adult
Differentiated
Cells e.g.
Blood, skin, bone

Types of stem cells

High capacity self-renewal

Pluripotent
Embryonic Stem Cell
Potential to make 'all' cell types

Committed Progenitor Adult Stem Cells
Limited capacity self-renewal
'Multipotent' - potential to make some cell types
e.g. Hematopoietic stem cells make blood cell
types
Mesenchymal stem cells make bones, cartilage,
connective tissue

Adult cells e.g. bone, cartilage
Types of stem cells

- High capacity self-renewal

Induced Pluripotent Stem Cell (iPSC)
Potential to make 'all' cell types

Adult cells e.g. bone, cartilage

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Nobel Prize October 2012
John Gurdon & Shinya Yamanaka
What is regenerative medicine?

Clinical applications focused on the repair, replacement or regeneration of cells, tissues or organs to restore impaired function.

Fibroblasts have been used to treat – venous stasis ulcers, diabetic ulcers, scar contractures, hypertrophic scars, stretch marks, acne scars, naso-labial folds & epidermolysis Bullosa erosions.

Fluorescent-labeled human fibroblasts
Source: Image courtesy of Intercytex

What are regenerative medicines?

Cells, chemicals (drugs) or biologics

Cell therapies may function transiently to deliver signals that
- stimulate a patient’s own stem cell-based repair system and/or
- exert an anti-inflammatory immuno-modulatory effect thus creating a better environment for natural repair processes

Cell therapies may engraft/transplant > replacing the diseased or damaged cells.
Where do cells for therapies come from?

**Mature cells** e.g. pancreatic islets, skin
- isolated from the living donor or cadaver
- derived from stem cells

**Adult stem cells** e.g. mesenchymal stem cells
- from bone marrow or cord blood

**Pluripotent stem cells** (embryonic/iPSC) - derived cells

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Where do cells for therapies come from?

- **Donor = Patient**
  - **Autologous**
    - Personalized Medicine
    - e.g. Chronic applications
  - **Allogeneic**
    - Could be one or multiple patients
    - ‘Off-the-shelf’
    - Acute & chronic
Cell therapies on the market

<table>
<thead>
<tr>
<th>COMPANY</th>
<th>PRODUCT</th>
<th>TARGET</th>
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</thead>
<tbody>
<tr>
<td>Shire (Advanced BioHealing)</td>
<td>Dermagraft</td>
<td>Skin</td>
</tr>
<tr>
<td>Altrika</td>
<td>MySkin</td>
<td>Skin</td>
</tr>
<tr>
<td>Avita Medical</td>
<td>ReCell</td>
<td>Skin</td>
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<tr>
<td>BioTissue Technologies GmbH</td>
<td>BioSeed-C</td>
<td>Cartilage</td>
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<tr>
<td>Dendreon</td>
<td>Provenge</td>
<td>Cancer</td>
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<tr>
<td>Euroderm</td>
<td>Epidex, Epigraft</td>
<td>Skin</td>
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<tr>
<td>Japan Tissue Engineering Co.</td>
<td>J-TEC Epidermis</td>
<td>Skin</td>
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<tr>
<td></td>
<td>Cartilage</td>
<td>Cartilage</td>
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<tr>
<td></td>
<td>Corneal Epithelium</td>
<td>Eye</td>
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<tr>
<td>Nuvasive</td>
<td>Osteocel Plus</td>
<td>Bone</td>
</tr>
<tr>
<td>Sanofi (Genzyme)</td>
<td>Epicel, Carticel</td>
<td>Skin</td>
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<tr>
<td></td>
<td>Cartilage</td>
<td></td>
</tr>
<tr>
<td>TiGenix</td>
<td>ChondroCelect</td>
<td>Cartilage</td>
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All Autologous except Dermagraft (allogeneic)

Cell therapy pipeline

<table>
<thead>
<tr>
<th>Year</th>
<th>Trials initiated</th>
<th>Completed</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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<tr>
<td>2005</td>
<td>13</td>
<td>0</td>
<td>10</td>
<td>2</td>
<td>0</td>
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<td>2011</td>
<td>25</td>
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<tr>
<td>Total</td>
<td>157</td>
<td>28</td>
<td>100</td>
<td>44</td>
<td>9</td>
</tr>
</tbody>
</table>

Clinical trial data for all major indications (excluding oncology)

Source: Alliance for Regenerative Medicine
The potential and impact of regenerative medicines

Regenerative medicines have the potential to:

- restore function ('cure')
- improve the condition (partial restoration of function)
- decrease the probability and/or timing of onset of co-morbidities

Impact?
- alter morbidity and mortality risk profiles

Predicted benefits:
- cost savings (cure/improved disease management)
- decreased claims (cure/improved disease management)
- new market access ('higher-risk' population)
- recover loss of economic productivity

Cell therapy industry challenges

<table>
<thead>
<tr>
<th>CHALLENGE</th>
<th>FEATURE</th>
<th>POTENTIAL IMPACT</th>
</tr>
</thead>
</table>
| Cost of Goods     | Cell-based regenerative medicines anticipated to be relatively expensive | Reimbursement status uncertain
                  |                                                                           | Limited uptake                                                                    |
                  |                                                                           | Shared-risk reimbursement models                                                  |
| Time to Benefit   | Maximal benefit anticipated to accrue over time (years)                 | Misalignment with budget cycles
                  |                                                                           | Reimbursement status uncertain                                                   |
                  |                                                                           | Limited uptake                                                                    |
| Evaluation        | Evidenced-based value proposition across multiple benefits              | Cost of complex clinical trials (multiple endpoints and time)                   |
                  |                                                                           | Data capture for co-morbidities and non-healthcare benefits                     |
| Business Model    | Product/service: market penetration and profit margins                  | Limited engagement by large corps                                               |
                  |                                                                           | Sub-optimal VC model                                                             |
                  |                                                                           | Alternative source of funding required                                          |
Limited Pharma engagement

2007 Novocell (ViaCyte) $25M led by JJDC
2007 Cellerix (merged TiGenix) $38M incl. Roche & Novartis Ventures
2008 EyeCyte $3M form Pfizer
2008 Pfizer launch regen med unit Cambridge UK/US
2008 HSCI/GSK collaboration $25M/5 yrs
2009 Athersys/Pfizer collaboration
2010 UCL/AstraZeneca collaboration
2010 iPierian $28M SR1, Biogen Idec
2010 Cephalon 20% Mesoblast for $220M ($1.7Bn milestone payments)
2011 Shire acquires Advanced BioHealing $750M (5x revenue)
2011 Pfizer spins-out Neusentis
2012 Shire acquires Pervasis Therapeutics deal worth up to $200M

Limited Pharma engagement – why?

Business model – unclear & different
Route to market relatively untested (“unknown unknowns”)
Limited Pharma engagement – impact?

Venture Capital

Sub-optimal venture capital model
Limited development capital for regenerative medicines
Interim summary

- Increasing & ageing population > Economic burden on healthcare and pensions provision.
- Chronic diseases are the leading causes of death and morbidity.
- Regenerative medicines:
  - potential to influence morbidity and longevity;
  - potential multiple benefits (health and productivity)
  - hurdles limit their market penetration
  - lack of adequate development capital

Key questions

1. Which industries have long-term perspectives on morbidity & longevity?
   - Re/insurance
   - Pension
2. How can regenerative medicines influence the value of re/insurance-product revenue?
3. What is the potential value?
4. Is the potential value a sufficient incentive to
   - support the development of regenerative medicines?
   - support the market penetration of regenerative medicines?
The potential impact of regenerative medicines
Case study: Targeting Types 1 and 2 diabetes

Cell therapy clinical trials for diabetes

*Results exclude clinical trials that have been withdrawn or terminated and those for which details are unavailable
Rapid progress in the clinic

Number of clinical trials targeting Type 1 Diabetes using either stem cells (green) or islets (red)

Estimated enrollment target for Type 1 Diabetes using either stem cells (green) or islets (red)

*Results exclude clinical trials that have been withdrawn or terminated and those for which details are unavailable

Probability of reaching the market?

Overall probabilities of success:
- Biologics: 26%*
- NMEs: 14%*
- Cell Therapies: Too early to determine (but consistent safety record)

If comparable to biologics 26% current active product-pipeline would predict the number of stem cell-based products to reach the market to treat:
- Type 1 Diabetes ~ 4
- Type 2 Diabetes ~ 3

*BIO/BioMedTracker BIO CEO & Investor Conference Feb 2011
Time to market?

Estimated primary completion dates for stem cell-based clinical trials targeting Type 1 Diabetes

Data source: clinicaltrials.gov

Time to market?

Autologous Transplantation Of Mesenchymal Stem Cells For Treatment Of Patients With Onset Of Type 1 Diabetes

Phase 2/3 Study
Primary completion date
July 2012 (25 month study)

Primary Outcome Measures:
C peptide release test
[Time Frame: 24 Months after intervention]
The concentration of C-peptide at 90 mins after the start of the C-peptide release test at 24 Months following the infusion or not with bone marrow mesenchymal stem cells

Data source: clinicaltrials.gov
Time to market?

Autologous Transplantation Of Mesenchymal Stem Cells For Treatment Of Patients With Onset Of Type 1 Diabetes

Phase 2/3 Study
Primary completion date
July 2012 (25 month study)

Regulatory preference for two Phase 3 trials?
Assume parallel studies > 5-6 years to market authorization?

2017-2018


Examples of cell therapies for diabetes
1. Stem Cell Educator

“….. a single treatment produces lasting improvement in metabolic control. Initial results indicate Stem Cell Educator therapy reverses autoimmunity and promotes regeneration of islet β-cells….”

Phase 2 – recruiting
➢ Estimated enrollment target 100
➢ Estimated study completion date Sept 2014

Data source: clinicaltrials.gov
Examples of cell therapies for diabetes
2. Embryonic stem cell – Derived Precursor Islets

Cells + Encaptra® - retrievable, non-biodegradable, vascularizing encapsulation technology that enables implanted cells to survive and differentiate into functioning islet cells.

Optimized for release of insulin in response to the recipient’s blood glucose

ViaCyte intends to test Pro-Islet in diabetic patients in a Phase 1 clinical trial in the foreseeable future.

Economic and insurance perspectives

John Woodford

Munich RE
Insurance perspective
Our first reactions    …show me the return

Life industry
• If regenerative medicine reduces mortality:
  – Improved profitability life insurance
  – Increased cost of annuities?
• Increased pool of insurable lives
• Opportunities for innovative rider products

Pensions industry

Are we net winners or net losers?
Or, is it simply a matter of timing?

Targeting conditions we care about

Source: univercellmarket, National Horizon Scanning Centre, Alliance for Regenerative Medicine
The Diabetes Epidemic
- trends and consequences

Conditions
- Severe hypertension
- Amputation
- Myocardial infarction
- Acute/chronic kidney failure
- Stroke
- Other vascular
- Eye disease

Even higher prevalence

The Diabetes Epidemic
- economic impacts

Health sector
- £10bn – 14bn

NHS expenditure
- £1bn (2012 prices)

Complications
Treatment & management
Diagnosis (small)

2010/11 2035/36


Employers
- £1bn?
- absenteeism
- ‘presenteeism’
- £3bn?

Patients and carers
- £5bn?
- unable to work
- withdrawing from work to care for family member
- early death

Economy
- lower productivity
- smaller lab. force
- lower profit, wages
- pension saving

Support
- care needs

State
- income support etc
- insurance
- income protection
- life

£5bn?

...currently 10% or more of NHS budget

Private health care and health insurance claims?
The Diabetes Epidemic
- key sources

- Hex N, Bartlett C, Wright D, Taylor M, and Varley D (2012) ‘Estimating the current and future costs of Type 1 and Type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs’, York Health Economics Consortium Ltd, University of York, York, UK (accepted for publication in Diabetic Medicine)

Why diabetes?....
...impacts lots of insurance products

- **Term Assurance**
  - A typical insurer might find:
    - ~1% applicants diabetic (Type I or II)
    - ~1:3 declined
    - Average premium double that of a healthy life

- **Critical Illness**
  - Diabetics (Type I or II) generally declined

- **Annuities**
  - Life expectancy (Men, Period)

  ![graph]

  - Eligibility for enhanced annuities?

The approach we are taking... 

...multi-state modelling

Healthy  |  Dead

Healthy  |  Dead

Diagnosed diabetic
The approach we are taking...

...multi-state modelling

Healthy → Diagnosed diabetic → Dead

Diseased state
- Severe hypertension
- Kidney failure
- Loss of limb
- Stroke
- Myocardial infarction
- Other vascular

State of control
- Good control
- Borderline control
- Poor control

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The approach we are taking... 

...multi-state modelling

Healthy → Diagnosed diabetic → Dead

x3

State of control

Good control

Borderline control

Poor control

Diseased state

Severe hypertension

Kidney failure

Loss of limb

Stroke

Myocardial infarction

Other vascular

Multiple diseases

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The challenges we are facing

Healthy → Diagnosed diabetic → Good control → Myocardial infarction → Dead

Estimating transition probabilities
• Need records of patient outcomes
• Possible sources:
  – GPRD
  – THIN
  – Q-Research
  – UKPDS Outcomes Model
  – Scottish Diabetes Study
• Access to most useful sources restricted and expensive

Impact on products
• Product take-up varies by SEC
• Need probabilities split by SEC

How you can help

• Share your thoughts and ideas with us today
• Do you have access to data which can help calibrate the models?
  – Co-morbidities
  – Benefit claims on health protection products
  – Costs of absenteeism
• Model-building and calibration

Working Group

Scientists

Actuaries

Economists
In summary

Cell therapies will change our marketplace:

- First generation of cell therapies are already on the market
- Significant pipeline of products in clinical development
- Cell therapy product pipeline aligned with drivers of protection claims and longevity
- Should expect more products come to the market within 10 years
- Development supported by UK Government initiatives e.g.:
  - Cell Therapy Catapult Centre (£50m over 5yrs)
  - Technology Strategy Board (£21.5m)
  - UK Regenerative Medicine platform (£25m)
  - Catalyst Fund (£180m including provision for Regenerative Medicine)

Possible support role for the life sector

- Development capital would accelerate products to market
- Is the insurance and pensions sector a potential long term investor?
- Innovative insurance products and reimbursement models could support the adoption of cell therapies

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Questions or comments?

Expressions of individual views by members of The Actuarial Profession and its staff are encouraged.

The views expressed in this presentation are those of the presenter.