Cell-based Therapies

Clinical Translation in Regenerative Medicine

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Regenerative Medicine Strategies

• **Intrinsic** repair: bolster the endogenous repair!...**Pharma**...

• When the intrinsic repair fails, **Extrinsic** repair:
  1. Engineered Cellular suspensions
  2. Combination products: cells/scaffold/growth factors
  3. Living tissues: tissue intermediates/provisional, full functional tissues/organs
Regenerative Medicine & Tissue Engineering

RESTORE TISSUE FUNCTION
REPLACE FAILING ORGANS
Gene Therapy

Biological medicinal product that contains a recombinant nucleic acid

• Aims to regulate, repair, replace, add or delete a genetic sequence
• The effect relates directly to the recombinant nucleic acid sequence or to the product of genetic expression of this sequence

E.g. medicine containing a gene carried by an adenovirus

Somatic cell therapies

Biological medicinal product that contains cells or tissues

• Aims to treat, prevent or diagnose a disease through the pharmacological, immunological or metabolic action of its cells or tissues

E.g. manipulated T cells for cancer therapy

Tissue engineered products

Biological medicinal product that consist of engineered cells or tissues

• Aims to regenerating, repairing or replacing a human tissue

E.g. artificial skin (burns), cell-based cartilage repair products, combination products
CELL-BASED THERAPIES IN REGMED

Overpromised and underdelivered : Why ??
The Reality

• Clinical benefit is variable, often hard to demonstrate
• In many cases, most cells administered die immediately
• Products may ‘misdifferentiate’
• Inadequate supply, poor manufacturing methods
Clinical Translation: Key Points

• **Unmet Medical Need**: define the patiënt!
  – Niche indications
  – Larger patient populations

• **Path of Clinical Development** (EMA/regulatory input ?)
  – Appropriate animal models
  – Safety data
  – Characterization of the product

• **Manufacturing**: can we make it?
  – The process is the product: understanding the product and its mechanism of action
  – Upscaling & industrial dimension
  – Quality BD, Cost BD

• **Path to the Market**: who will pay for it?
2 examples ....

Some progress in the translation from patient to bench and back to the bedside....
Example 1: Cell-based approach aimed at durable regeneration of knee cartilage

The clinical problem

Repair of single symptomatic cartilage defects of the femoral condyle of the knee (ICRS grade III or IV) in adults.
Regenerative solutions to bridge the gap

Symptom relief
- Pain killers
- Adapt lifestyle

Regeneration
- Microfracture
- Debridement

Replacement
- Joint revision
- Joint replacement

Severity of symptoms

Time: duration of symptoms
Autologous Chondrocyte Implantation for the repair of a symptomatic joint surface defect
## Characterization of the Product

<table>
<thead>
<tr>
<th>Test</th>
<th>Method</th>
<th>GMP goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identity</td>
<td>Morphology</td>
<td>Quality, Safety</td>
</tr>
<tr>
<td></td>
<td>Molecular markers</td>
<td></td>
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<tr>
<td>Dose</td>
<td>Viable cell number</td>
<td>Quality, Efficacy</td>
</tr>
<tr>
<td>Potency</td>
<td>Relevant bioassays: <em>can the cell product make Hyaline cartilage in vivo?</em></td>
<td>Efficacy</td>
</tr>
<tr>
<td>Purity</td>
<td>Inappropriate cell contamination</td>
<td>Safety</td>
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<tr>
<td></td>
<td>Residual impurities</td>
<td></td>
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<tr>
<td>Safety</td>
<td>Sterility</td>
<td>Safety</td>
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<tr>
<td></td>
<td>Mycoplasma</td>
<td></td>
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<tr>
<td></td>
<td>Endotoxins</td>
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<td></td>
<td>Adventitious viruses</td>
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</table>
Study hypothesis & outcome

Superiority on structural repair parameters at 12 months as precursor of long term clinical benefit

Durable repair & long term clinical benefit

Comparable short term clinical outcome

Primary endpoints
Long-term follow-up

Follow up: Baseline Short-term Long-term

Improvement from baseline

ChondroCelect
Microfracture

Superiority on structural repair parameters at 12 months as precursor of long term clinical benefit
Characterized Chondrocyte Implantation Results in Better Structural Repair When Treating Symptomatic Cartilage Defects of the Knee in a Randomized Controlled Trial Versus Microfracture

Daniel B. F. Saris, MD, PhD, Johan Vanlauwe, MD, Jan Victor, MD, Miroslav Haspl, MD, PhD, Michael Bohnsack, MD, Yves Fortems, MD, Bruno Vandekerckhove, MD, K. Frederik Almqvist, MD, PhD, Toon Claes, MD, Frank Handelberg, MD, Koen Lagae, MD, Jan van der Bauwhede, MD, Hilde Vandenberghen, MD, K. Gie Auw Yang, MD, PhD, Mirsad Jelic, MD, PhD, Rene Verdonk, MD, PhD, Nancy Veulemans, Ir, Johan Bellemans, MD, PhD, and Frank P. Luyten, MD, PhD

Conclusion: One year after treatment, characterized chondrocyte implantation was associated with a tissue regenerate that was superior to that after microfracture. Short-term clinical outcome was similar for both treatments. The superior structural outcome may result in improved long-term clinical benefit with characterized chondrocyte implantation. Long-term follow-up is needed to confirm these findings.

The American Journal of Sports Medicine, Vol. 36, No. 2
Conclusion: Characterized chondrocyte implantation for the treatment of articular cartilage defects of the femoral condyles of the knee results in significantly better clinical outcome at 36 months in a randomized trial compared with MF. Time to treatment and chondrocyte quality were shown to affect outcome.
PRESS RELEASE
European Medicines Agency recommends first marketing authorisation for an advanced therapy medicinal product

The European Medicines Agency has recommended the first marketing authorisation for an advanced therapy medicinal product, following a positive opinion from the Agency’s Committee for Advanced Therapies (CAT) and the Committee for Medicinal Products for Human Use (CHMP).
Whom to treat?

Patients at risk and responders to treatment!
The micro-environment is as important as the “living” drug
5 year follow up: subgroup analysis

Overall KOOS
< 3 yrs since onset of symptoms

Overall KOOS
≥ 3 yrs since onset of symptoms

* P < 0.05
AUC 24-60M  p 0.04
Business case...

- **Orphan** indication
- **Cost effectiveness?** reimbursement in BE and NL is linked to registry data
  - Use in daily **clinical practice**
- Parallel market in Europe under **Hospital Exemption**
- **Withdrawal** of the market
EXAMPLE 2
Unmet medical need: Large long bone defects

Small defect: biomaterials, bone fillers
- Cell recruitment OK
- Time OK
- # cells OK
- Clinical relevance for small defects

Larger defects: e.g. BMP technology
- Cell recruitment
- Cell Proliferation
- Differentiation
- Tissue formation
- Integration....Healing

Large (≥ 4 cm) & Compromised environment:
- Cell-based ATMP
- Recruitment for implant integration only
- Volumetric tissue formation

Large long bone defects
- Cell recruitment OK
- Clinical relevance for small defects

Unmet medical need: Large long bone defects
Scientific Basis: manufacturing a Callus

Lenas et al, TE 2009; Nilsson et al., submitted
Clinical Translation: Scaling

• Scale-up & manufacturing for large tibial defect
  – 3 cm rabbit
  – 4-5 cm in sheep
  – Up to 10 cm in patients

35mm$^3$ → 40x volume increase → >1400mm$^3$
The large animal models

Orthotopic

Feasibility
Safety
Efficacy
Define the Outcomes

16 weeks after implantation ATMP

20 weeks after monofix installation

6 months after removal monofix
New Frontier: 3D living implant

MANUFACTURING CHALLENGES REQUIRING TECHNOLOGY DEVELOPMENTS
Engineering into Life Sciences

• Key enabling technologies: lab visit
  – bioreactors
  – biosensors
  – non invasive imaging
  – 3D- bioprinting
  – Computational modeling
  – Control software, database handling
  – Quality assurance system
  – .........
Bioreactor systems

Major achievements:
• Two temperature controlled chambers
• Incubator separated in gas exchange and heating module and dry environment
Non destructive, quantitative imaging: CE-CT

Simultaneous visualization of mineralized and soft skeletal tissues

Quantification of bone marrow adiposity and
Software

MyCellHub
Streamlining cell production processes
Manufacturing at the core....
GMP manufacturing ....

GMP Manufacturing Platform

Process
- Scalable bioreactor culture
  - Closed, monitored and controlled
- Scalable Robotic culture of microtissues
- Designed bioprinting of personalised living implants

Product
- Single stem/progenitor cells on microcarriers
- Cartilage intermediate microtissue formation and maturation
- Large ATMP Bone regeneration
- Complex ATMP osteochondral

Analytics
- pH, Gluc, DOT, omics information on single cells
  - Guarantee efficiency
- Imaging, biosensing (MeMS), Raman, omics
  - Differentiation cells and ECM
  - Monitor and guarantee Potency
- Raman, Imaging
  - Guarantee viability

Generic application
- Spheroid-Based TE ATMPs
Bioprocess Development

Single cell expansion

Automated µtissues

ATMP bioassembly

KU LEUVEN

CATAPULT
Cell and Gene Therapy

Fraunhofer

KU LEUVEN

paa
peak analysis & automation

Maastricht University
MERLN Institute

Wyss Institute
The Integrated Manufacturing Line: Vision!
Many points to develop!

BUILDING A COMMON VISION...
How to become successful?

- Critical mass: Public-private partnerships
- Define the patient and engage the patient organisations
- Talk early on to regulatory bodies: adapt regulatory path??
- Talk early on with reimbursement agencies
- Translational, interdisciplinary platforms in academia
RegMed XB

• Innovative Collaborations to solve chronic diseases
An ecosystem is emerging NL/FL around regenerative medicine

Organizations in the Netherlands and Belgium – selection of new and existing players

Source: Company websites
QUESTIONS ?