Challenges in development and approval: the case of cell based therapeutics

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BBS / PSI 1-Day Scientific Meeting:
Empower the immune system to fight cancer
06, 2016
Content

1. Background information of cell based ATMPs
2. General concept and common hurdles in early and late stage manufacturing, non-clinical and clinical development
3. The Zalmoxis case study: suicide genetically modified cells for post-BMT in leukemia patients
Definitions of Cell based therapeutics

• Contain or consist of a recombinant nucleic acid or Autologous, allogeneic, or xenogenic use living cells
• More than minimally manipulated cells or tissues
• Combined with other components - growth factors, inert matrices, mechanical devices
• Systemically active: effects beyond site of transplantation
• Non-homologous use: application not similar to original tissue function
Organization developing Biologics & ATMPs are different

- Small and medium enterprises (SME)
- Non profit organization (Hospital, Academia and Foundations)
- 40% from SMEs, academia, public bodies and public-private partnerships
- 61% orphan designation drug from SMEs
# Current status for MA of ATMPs in EU

## Authorized products

<table>
<thead>
<tr>
<th>Product</th>
<th>Holder</th>
<th>Date</th>
<th>Therapeutic area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chondrocelect</td>
<td>Tigenix</td>
<td>10/2009</td>
<td>Cartilage disease</td>
</tr>
<tr>
<td>MACI (R)</td>
<td>Combined</td>
<td>06/2013</td>
<td>Fractures, Cartilage</td>
</tr>
<tr>
<td>Provenge (R)</td>
<td>Dendreon UK</td>
<td>10/2013</td>
<td>Prostatic Neoplasms</td>
</tr>
<tr>
<td>Glybera (E)</td>
<td>UniQure</td>
<td>10/2012</td>
<td>Hyperlipoproteinemia Type (E)</td>
</tr>
<tr>
<td>Holoclar</td>
<td>Chiesi</td>
<td>12/2014</td>
<td>Ocular burn</td>
</tr>
<tr>
<td>Imlygic (T-Vec)</td>
<td>Amgen</td>
<td>10/2015</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Strimvelis</td>
<td>GSK</td>
<td>04/2016</td>
<td>ADA syndrome</td>
</tr>
<tr>
<td>Zalmoxis</td>
<td>MolMed</td>
<td>08/2016</td>
<td>ALL</td>
</tr>
<tr>
<td>Spherox</td>
<td>Co.Don.Ag</td>
<td>05/2017</td>
<td>Muscolo-skeletal system</td>
</tr>
</tbody>
</table>

## Products under evaluation

<table>
<thead>
<tr>
<th>Product</th>
<th>Applicant</th>
<th>Application</th>
<th>Therapeutic area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expanded Mesenchymal Cells</td>
<td>TiGenix</td>
<td>Sept 2015</td>
<td>Perianal Fistulas</td>
</tr>
</tbody>
</table>
## ATMPs & large molecules are different

### Manufacturing

<table>
<thead>
<tr>
<th>Biologics</th>
<th>ATMPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Produced by host cells</td>
<td>Cell or virus is the product</td>
</tr>
<tr>
<td>Process product specific</td>
<td>Patient specific</td>
</tr>
<tr>
<td>Large batches</td>
<td>Small batches</td>
</tr>
<tr>
<td>Terminal sterilization</td>
<td>No terminal sterilization</td>
</tr>
</tbody>
</table>

### Structure and characterization

<table>
<thead>
<tr>
<th>Biologics</th>
<th>ATMPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>High M.W.</td>
<td>No M.W. defined</td>
</tr>
<tr>
<td>Mass activity Balance (µg, IU)</td>
<td>Cell/kg, MOI, Viability</td>
</tr>
<tr>
<td>Product degradation</td>
<td>Unwanted cell population</td>
</tr>
</tbody>
</table>

### In vivo behavior

<table>
<thead>
<tr>
<th>Biologics</th>
<th>ATMPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>MABEL</td>
<td>Effective dose</td>
</tr>
<tr>
<td>p450 degradation system</td>
<td>Long time resident</td>
</tr>
<tr>
<td>PK and TK</td>
<td>Biodistribution</td>
</tr>
<tr>
<td>Carcinogenicity, mutagenesis</td>
<td>Tumorigenicity and insertional mutagensis</td>
</tr>
<tr>
<td>Developmental toxicity</td>
<td>Vertical transmission</td>
</tr>
</tbody>
</table>

### Clinical development

<table>
<thead>
<tr>
<th>Biologics</th>
<th>ATMPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large, Blind, randomized pivotal trial</td>
<td>Unblind (non-randomized) pivotal trial</td>
</tr>
<tr>
<td>Standard design</td>
<td>Adaptative design</td>
</tr>
<tr>
<td>FIM → Ph I → Ph II → Ph III → MA</td>
<td>FIM → (Ph I/II → (Ph III)) → MA</td>
</tr>
<tr>
<td>Full MA</td>
<td>Conditional, Exception MA</td>
</tr>
<tr>
<td></td>
<td>PASES, Registry establishment</td>
</tr>
</tbody>
</table>
Issues in manufacturing & quality

• Labour intensive
• Non terminally sterilized product
• Process with high rate of changes during development and comparability
• Availability of GMP-grade auxiliary material and reagents
• Characterization of the product (and intermediates)
  – Orthogonal design for QC test panel and acceptance limit definition
  – Specific ad hoc test (for potency) to be set up and validated
  – Device and or matrix characterization for combined products
  – Not fully tested MP for patient administration
  – Extent of assay validation
  – Defining / Refining specs
• Traceability as integrated system
• Logistics and overall organization
• Scale up model to accommodate increase numbers in late development post-approval
Scale up and scale out models

VECTOR MANUFACTURING - A SCALE UP MODEL

T CELL TRANSDUCTION - A SCALE OUT MODEL

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Changes in manufacturing: comparability

Highly similar / Similar → No Impact on safety / efficacy → No need of additional studies

Product Specific

Comparability assessment

Process Specific

Analytical Capability

Some differences
Analy proc insufficient → Possible impact / Unknown impact → Need of in vivo studies

Adapted by Jia Audrey - Regulatory Perspective on Comparability Assessments of Biotechnology Products

Business or Operating Unit/Franchise or Department
The comparability puzzle

Jia Audrey - Regulatory Perspective on Comparability Assessments of Biotechnology Products
The comparability dilemma: of apples and oranges

The same?

P. Lucas: Implications and regulations of changes during product & process development – TOPRA Msc 2014
Non Clinical development

• Non clinical development of ATMPs follows non-conventional paths

• Non clinical development is designed on a case by case basis
  – Biology of the product
  – Presence of genetic modification

• Non clinical development or toxicology?

• Use of published data supportive of limited non-clinical data set

• Routine QC analysis supportive for safety assessment
Non clinical development

- Standard tox studies and paradigm for safety evaluation hardly applicable to cell based products
- Concurrent efficacy and safety assessment

**ADME**
- Cell persistence
- Viral shedding
- Cell homing / migration
- Vertical transmission

**Repeated dose Tox**
- Repeated dosing?

**Carcinogenicity**
- Insertional Mutagenesis
- Cell transformation
- Clonogenic assays
- Use of specific tumour prone animals
Issues in non-clinical development

• Extent of non clinical studies
  – Pre-existing clinical data
  – Previous non-clinical data with the same product

• Duration of studies
  – Difficult to establish in long life resident products
  – Dependant to long term expected effects
  – Large animals longer life expectancy than smaller animals

• Choice of relevant animal model
  – Homologous / disease animal model for PoC studies
  – Immunosuppressed animals

Tailored, case by case and risk-based approach
Clinical

• The specific requirements are linked to the biologic characteristics of the product
  – Dependency / reactivity to micro-environment
  – Differentiation / de-differentiation processes
  – Migration

• Patient population and indication
  – Orphan and ultra-rare indication
  – Non conventional statistics and design

• FIM and Phase I/II studies
  – Disease patients
  – Concurrent safety / efficacy endpoint

• Logistics issues
  – Delivery and Supply chain
  – Storage at the site
# Tools for expedite clinical development and registration: adaptive licensing

<table>
<thead>
<tr>
<th>EU</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRIME / Accelerated assessment</strong></td>
<td><strong>Breakthrough therapy</strong></td>
</tr>
<tr>
<td><strong>Conditional Marketing Application</strong></td>
<td><strong>Accelerated Assessment</strong></td>
</tr>
<tr>
<td><strong>Exceptional circumstances</strong></td>
<td><strong>Fast track</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Priority review</strong></td>
</tr>
</tbody>
</table>

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**Adaptive Licensing**

- Current model of licensing: "The Magic Moment"
- Evidence vs. access tradeoff
- Adaptive Licensing

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**EU US**

- PRIME / Accelerated assessment
- Conditional Marketing Application
- Exceptional circumstances
- Breakthrough therapy
- Accelerated Assessment
- Fast track
- Priority review

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[Image: Diagram illustrating adaptive licensing]

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**Business or Operating Unit/Franchise or Department**

16 Business Use Only

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**NOVARTIS**
ATMPs can be licensed with restrictions and with limited clinical data

<table>
<thead>
<tr>
<th>Product / clinical development</th>
<th>Holder</th>
<th>Therapeutic area</th>
<th>Post MA Commitments</th>
</tr>
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<tbody>
<tr>
<td>Chondrolect</td>
<td>Tigenix</td>
<td>Cartilage disease</td>
<td>NA</td>
</tr>
<tr>
<td>MACI (R)</td>
<td>Genzyme</td>
<td>Fractures, Cartilage</td>
<td>NA</td>
</tr>
<tr>
<td>Provenge (R)</td>
<td>Dendreon</td>
<td>Prostatic Neoplasms</td>
<td>Registry establishment, Results of on-going clinical trial clinical study for distant metastasis</td>
</tr>
<tr>
<td>Glybera (E)</td>
<td>UniQure</td>
<td>Hyperlipoproteinemia Type (E)</td>
<td>Registry establishment, Improve viral safety, Assay validation New clinical study on 12 patients</td>
</tr>
<tr>
<td>Holoclar</td>
<td>Chiesi</td>
<td>Ocular burn</td>
<td>Educational material, Completion of interventional study</td>
</tr>
<tr>
<td>Strimvelis</td>
<td>MolMed</td>
<td>ALL</td>
<td>Educational material, PASS Study with registry Completion Phase III</td>
</tr>
<tr>
<td>Zalmoxis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Clinical challenges

• Pivotal Phase III studies
  – Prospective, randomized CT expected, but difficult to achieve
  – Control arms difficult to establish
  – Multicenter (multinational) vs monocentre studies
  – Dose selection and justification

• Confounding factors
  – Administration procedures (e.g. surgery)
  – Hospital procedures for manufacturing
  – Concomitant, non standardized therapies (immunosuppression)

• Non conventional design & stats
  – Orphan diseases
  – Bayesian statistics and adaptive designs

• Known risks
  – Infections
  – Immune / Inflammatory reactions
  – Tumourigenicity
  – Off-target transduction

• Pharmacovigilance
  – Study duration: long follow up and risk management
  – Safety and efficacy endpoints
Issues in manufacturing & quality

Adapted from Jia Audrey - Regulatory Perspective on Comparability Assessments of Biotechnology Products

<table>
<thead>
<tr>
<th>Raw material low quality</th>
<th>Validated safety analytical tests</th>
<th>Limited process validation data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety studies including PK</td>
<td>Set up of in vivo model PoC studies in homologous model</td>
<td></td>
</tr>
</tbody>
</table>

Increase product understanding
Increased raw material quality
Potency tests set up and initial validation
• Process changes to accommodate increased production rate
• Changes in raw materials
• Formulation changes
• Development towards a more closed manufacturing process
• Identify PC and CQA
Non-clinical data to address Repro Tox (if applicable)
Insertional mutagenesis

Full analytical validation
Formal stability study
Complete process characterization and validation
Process changes
Ensured supply chain
Ideal closed manufacturing process
Alternate supplier for critical raw materials
Complete cell chain identity
In use and shipping stability
Educational material in place

FIM
Before Pivotal study
Late phase / post MA

Emphasis is primarily on product safety
Emphasis on product safety and efficacy

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Zalmoxis – a CB therapy for leukemia

Indication: post-BMT adjunctive treatment for HR AML & ALL w/o HLA-matched family or unrelated donor
Regulatory and clinical development

- TK007 - Phase I/II
  - 2002: CTA
  - 2004: OD EMA
  - 2005: PA EMA
  - 2007: OD USA
  - 2008: PA EMA
  - 2011: CTA
  - 2012: PA EMA
  - Changes for DS manufacturing

- TK007 - Phase I/II Extension
  - 2009: CAT Advice
  - 2010: IND
  - 2011: EoP II meeting
  - 2012: PA EMA
  - Vector process scale up DS process changes

- TK008 - Phase III
  - 2012: PA EMA
  - Conditional MAA

- Timeline:
  - 2002: CTA
  - 2003: OD EMA
  - 2004: PA EMA
  - 2005: OD USA
  - 2007: PA EMA
  - 2008: CTA
  - 2009: CAT Advice
  - 2010: IND
  - 2011: EoP II meeting
  - 2012: PA EMA
  - 2014: Conditional MAA

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NOVARTIS
## IMP development

<table>
<thead>
<tr>
<th>Vector Manufacturing</th>
<th>Pre-Phase I/II</th>
<th>Phase I/II</th>
<th>Phase III</th>
<th>Future developments</th>
</tr>
</thead>
<tbody>
<tr>
<td>SFCMM3 #16</td>
<td>SFCMM3 #35</td>
<td>SFCMM3 Mut2 #48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell Factories</td>
<td>Roller bottle</td>
<td>30 Lt fermentor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roche 82.1 Anti-LNGFR MoAb</td>
<td>MM Anti-LNGFR 20.4</td>
<td></td>
<td></td>
<td>Anti-LNGFR 20.4 SFM</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lymphocytes manipulation</th>
<th>Pre-Phase I/II</th>
<th>Phase I/II</th>
<th>Phase III</th>
<th>Future developments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHA</td>
<td>OKT-3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-Culture</td>
<td>Spinoculation</td>
<td>Retronectin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Open Sysytem</td>
<td>CMS</td>
<td></td>
<td>Fully automated system</td>
</tr>
<tr>
<td></td>
<td>14 Day process</td>
<td>10 day process</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Viable cells adm</td>
<td>Frozen formulation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Non clinical development for Zalmoxis

In vivo studies

- Test system: mice with immunological defects to enable xenograft

  PD
  - Engraftment
  - TK expression
  - Suicide effectiveness
  - T cell differentiation

  PK
  - Biodistribution

  Toxicology
  - Long term Tox
  - Oncogenicity
  - Local tolerance

  Comparability

In vitro studies

  PD
  - T cell polarization
  - Antigen activation

  Safety - Oncogenicity
  - TCR analysis
  - Vector integration
  - RCR detection

Business or Operating Unit/Franchise or Department
# Zalmoxis design for in vivo studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal Model</th>
<th>Endpoints</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>NOD-SCID</td>
<td>Mortality, Engraftment, GvHD, Long term safety, GvHD rescue</td>
<td>PBMC / PBL, Saline</td>
</tr>
<tr>
<td>Study 2</td>
<td>Humanized NOD-SCID</td>
<td>Mortality, Engraftment, GvHD, Biodistribution</td>
<td>PBL, Saline</td>
</tr>
<tr>
<td>Study 3</td>
<td>NSG</td>
<td>Comparability: • Engraftment, • GvHD, • Mortality</td>
<td>PBMC Mock transduced, Saline</td>
</tr>
</tbody>
</table>
Clinical Development – Phase I/II

Single arm, non randomized open label study
Patients with haematological malignancies
aGvHD: 10 out 30 pts (33%), 1 cGvHD

30 TK treated (17 fresh; 13 frozen)
22 IR
8 no IR

TK cells engraftment

Infectious AE

T cell repertoire by spectratyping


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Clinical: Pivotal Phase III Study

• Primary endpoint: Leukemia-free survival
• Secondary endpoints:
  – NRM, overall survival, relapse, disease-free survival
  – immune-reconstitution, engraftment,
  – aGvHD, cGvHD, infectious, safety,
  – quality of life, pharmacoconomics
• Control Arm
  – T-cell depleted haplo +
  – Un-manipulated haploidentical BMT with post-BMT cyclophosphamide (Luznik 2010)

Source: EMA EPAR for Zalmoxis CMA approval
Thank you