Raw Materials for ATMP Manufacturing: Quality, regulatory and supply issues

AMC Workshop GMP FOR ATMP DISCUSSION DAYS
Manchester, 08.03.2018
Our Mission is
to enable and accelerate
safe and efficient transition of
cell, gene and tissue engineered products
from preclinical to
post-approval clinical applications
for the benefit of patients worldwide

- 20 years advanced expertise in GMP manufacturing and regulatory affairs in cell & gene therapy
- HQ, GMP facility and R&D labs in Freiburg, Germany
- USA subsidiary near Boston
- 60+ employees
- Worldwide distribution of products
Cellular and Molecular Therapeutics

GMP Processing of Cell Therapy Products
- Manufacturing license 1995
- HSC, cord blood stem cells, DC, chondrocytes, etc. (> 10,000 cell products processed)

> 15 years in-house GMP experience

GMP Manufacturing of Recombinant Protein Pharmaceuticals
- Manufacturing license 2001
- Patient specific idiotype vaccine for phase I/II lymphoma trials
- GMP contract manufacturing service for phase I/II

> 10 years in-house GMP experience

⇒ Know-how used to establish GMP reagent manufacturing
Products and Services

*Positioning in Cell Therapy Workflow*

ADCF and Serum-free GMP Products for:
- Optimal Safety
- Optimal Consistency
- Optimal Cost-effectiveness

- Isolation
- Selection
- Gene Transfer
- Cell Culture (• Expansion • Differentiation)
  - ADCF Cytokines
  - Serum-free Media
  - Supplements & Cells
  - VueLife® Bags
- QC
- Storage
  - KryoSure®
  - Cryopreservation bags
- Administration
# Product Portfolio

*Complete Sets of Reagents for Clinically Relevant Cell Types*

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Reagents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematopoietic stem cells (HSC)</strong></td>
<td>TPO, SCF, Flt-3L, IL-3, IL-6</td>
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<tr>
<td></td>
<td>SCGM Medium</td>
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<tr>
<td><strong>Dendritic cells (DC)</strong></td>
<td>IL-1β, IL-4, IL-6, IL-10, GM-CSF, TNFα</td>
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<tr>
<td></td>
<td>DC Medium</td>
</tr>
<tr>
<td><strong>T cells</strong></td>
<td>IL-2, IL-7, IL-10, IL-15, IL-21, TGF-β1</td>
</tr>
<tr>
<td></td>
<td>XF/CD Medium under development</td>
</tr>
<tr>
<td><strong>NK cells</strong></td>
<td>IL-2, IL-7, IL-15, IL-21</td>
</tr>
<tr>
<td></td>
<td>SCGM Medium</td>
</tr>
<tr>
<td><strong>Chondrocytes</strong></td>
<td>FGF2, PDGF-BB</td>
</tr>
<tr>
<td></td>
<td>Gelatin</td>
</tr>
<tr>
<td><strong>Mesenchymal stromal cells (MSC)</strong></td>
<td>FGF2, TGF-β1, EGF, PDGF-BB</td>
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<tr>
<td></td>
<td>MSC Medium, Gelatin</td>
</tr>
<tr>
<td><strong>ESC, iPS cells</strong></td>
<td>FGF2, TGF-β1, Act A, EGF, OSM, HGF</td>
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<tr>
<td></td>
<td>Further cytokines for expansion and differentiation <strong>coming soon</strong></td>
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<tr>
<td></td>
<td>Adhesion factors <strong>under development</strong></td>
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</table>

*... more in the Pipeline*
Raw / Ancillary Materials for ATMP Manufacturing

Regulatory Background

1. Isolation & Selection

2. Cell Processing

Ancillary Material (AM) / Raw Material (RM)
- Growth factors, cytokines
- Media and supplements, buffers

*Not intended to be, but may become part of the final product!*

3. Quality Control

4. Administration

Qualification of AM + Vendor

Final Product
- Stability
- Safety
- Potency
- Purity
Raw / Ancillary Materials for ATMP Manufacturing

Regulatory Background

US Guidance

<1043> „AM for Cell, Gene and Tissue-Engineered Products”
- AM Qualification, AM Risk Classification, AM Performance Testing & AM Residual Level Assessment
- Risk classification (Tier 1 to 4, qualification and risk reduction activities)
- CellGenix GMP products can be classified in Tier 2: "Low-risk, well-characterized material with intended use as AMs, produced under relevant cGMPs."

<92> „Growth Factors & Cytokines Used in Cell Therapy Manufacturing”
- rh Interleukin 4, reference standard available
- CellGenix was involved in drafting this document together with the USP
Raw / Ancillary Materials for ATMP Manufacturing

Regulatory Background

EU Guidance


- Risk Assessment, Origin of Raw Materials, Production, General Quality Requirements, Storage & Labelling
- Sera and Serum Replacements, Proteins produced by recombinant DNA Technology, Proteins extracted from biological material, Vectors

Guideline on GMP specific to ATMPs, Eudralex Vol. 4, Part IV (Adopted 22 November 2017)

- Minimal Raw Material Specification, Compliance verification, Contamination, Labelling, Release & Traceability
- “As far as possible, raw materials used in the manufacturing of ATMPs should take into consideration the Ph. Eur 5.2.12 general chapter on raw materials of biological origin [...].”
Raw / Ancillary Materials for ATMP Manufacturing

Regulatory Background

ISO Technical Committee 276 Biotechnology, Working Group 4 Bioprocessing

Technical Standard 20399 on Ancillary Materials (work in progress):
- Part 1 General definitions and requirements
- Part 2 Best practice guide for suppliers
- Part 3 Best practice guide for users

Contents include:
- Animal-derived components
- Mutual Responsibilities
- Quality Management Systems
- Characteristics & Quality Attributes
- Manufacturing & Biosafety
- Performance
- Documentation
- Quality Declarations
- Evaluation & Risk Mitigation
- Characterization of biologicals
- Managing Changes

First global technical standard for Ancillary / Raw Materials
CellGenix CellGro® GMP Grade Products

**Major Quality Attributes**

- **Safety**
  - Raw material and supplier qualification
  - ADCF policy and serum-free policy

- **Purity, Potency, Consistency, Stability**
  - GMP compliant manufacturing

- **Regulatory Compliance and Support**
  - Full documentation
  - Technical and Regulatory Support

⇒ **Suitability for Intended Use**
  - Clinical ex vivo cell processing
Major Quality Attributes

**ADCF and Serum-Free Policy**

**Serum-Free Policy:**
No media human or animal serum and part of any media product, all media are intended to be used in serum-free protocols

**ADCF Policy:**
No animal or human-derived components are part of any cytokine product

- Applies to majority of CellGenix® Cytokines
- Produced in dedicated animal-free facility
- No need of additional viral safety measures

**ADCF Level 1**
- ADC Production Area: No ADC in product, but ADC in production process
- Documented evidence of viral / prion safety
- Demonstrated virus reduction capacity of manufacturing process

**ADCF Level 2**
- Animal-Free Facility: No ADC in product and production process
- Pharmaceutical grade ADC whenever feasible
Major Quality Attributes

Manufacturing and QC following GMP Guidelines

**GMP Grade:** manufactured, tested and released following the relevant GMP guidelines, including:

- Manufacturing and QC according to SOPs, qualified and trained personnel
- Clean room facility and qualified equipment
- Validated and consistent processes (manufacturing, cleaning, QC), including
  - Characterized MCB/WCB and plasmid banks
  - Consistency batches
  - In-Process Controls (IPC) at each manufacturing step
  - Validated analytical methods
  - Depletion of critical impurities (host cell protein, endotoxin, DNA)
- Stability program (stress, accelerated, real-time, etc.)
- CAPA System: OOS, deviations and change management
- Functional QC testing with relevant cell culture assays
- Product release by QC according to specifications
Major Quality Attributes

Regulatory Compliance & Support

Regulatory Compliance

- cGMP and ICH (certification not possible)
- Ph. Eur. 5.2.12, USP <1043>, USP <92>
- ISO Technical Standard on AM (in preparation)

Regulatory Office and Customer Support

- Continuous interaction with major regulatory authorities
- Expert regulatory and technical support
- Product information: batch specific CoA, data sheet, MSDS, TSE-sheet
- Drug Master Files for cross-reference
- Regulatory support files (in preparation, please inquire)
- Proactive change notification
- On-site audits, Quality Agreements
GMP Processing of Cell Products

Right Time for Process Changes?

ATMP manufacturers should identify appropriate RM/AM and reliable suppliers in time.
From Research to ATMP
The Highest Quality for each Step in the Process

**Preclinical Grade:** Major product characteristics of the GMP product (expression system, production steps, performance)

**GMP Grade:** manufactured, tested and released following the relevant GMP-guidelines, regulatory documents and support available
Supply Chain Security

Facility Expansion

Facility Extension 1300 m²
- R&D Laboratories
- QC Laboratories
- Warehouse and Logistics

GMP Protein Production
- Automated Filling Line
- Doubled capacity for Bulk Production

Expansion finalized in 2018

Prepared for supply agreements
Cell, Gene Therapy and Regenerative Medicine

Network of Interacting Protagonists

Our Contribution as Supplier of AM / RM

- Innovative products to enable transition from preclinical to clinical application
- High consistent, predefined product quality
  - Safety, potency, purity, stability
  - Suitability for intended use
- Expert regulatory and technical support
- Supply chain security
  - Investment in capacity expansion
  - Supply Agreements
- Trusted partner with over 20 years expertise
  - GMP manufacturing
  - Cell & gene therapy
Thank You For Your Attention