Industry Focus Meeting
February 25, 2016

Resources

Agenda

Meeting Objectives:
(1) Update on government solicitation
(2) Review manufacturing impact topics (MITs);
(3) Develop proposal for government solicitation;

9-10AM	Continental Breakfast
10-10:30AM	Welcome, Recap, and Updates Review manufacturing impact topics (MITs) Charge for the day: government solicitation
	MIT Working Groups: Session 1
10:30am-11:30am	Topic Groups Session 1: 1. Media 2. Bioreactors 3. Preservation
11:30am-12pm	Reports and General Discussion from Session 1
12-12:45pm	Working Lunch / Innovation Center Structure
	MIT Working Groups: Session 2
12:45pm-1:45pm	Topic Groups Session 2: 4. Manufacturing 5. QC
1:45-2;15pm	Reports and General Discussion from Session 2
2:15pm	Closing Remarks
2:30pm	Adjourn

Manufacturing Impact Topics (MITs): Media

Problem: There are numerous challenges facing the field: Serum is variable in performance and constitution, and availability in quality levels suitable for cell therapy manufacturing is limited. There is a high cost of the synthetic growth factors and other components to replace media components that may cost-prohibitive, especially at smaller scales. Quite often one complete medium formulation will not work due to variability of the cells**.** Different cells have different nutrient requirements so a universal medium may not be possible for all cell types. There are challenges pertaining to media replenishment and toxicity. Scalability of media to different culture conditions is another challenge in addition to stability, shipment and format of the media. These last points need to be addressed at an international level. There are also international regulatory issues and safety standards that are not well defined.

Solution: There were four main solutions that we identified at our second Industry focus meeting where 5 companies (EMD Millipore, Cord Blood Registry, Akron, BD Technologies, and ThermoFisher) formed a break out group to develop these solutions that would be achieved over a 5 year period. The first solution is to pilot a program with a specific cell type (MSC) and go through the process: (a) Test or develop a defined media, (b) Identify and test small molecule substitutes for growth factors, (c) Test multiple donors and tissue types, (d) Define QC testing of stability and functionality of the cells, (e) Reduce metabolite toxicity, and (f) Identify viral inactivation technologies that do not affect media attributes. The second solution is to define serum albumin: (a) Identify the components, (b) Reverse manufacture serum albumin, and (c) Test functionality. The third solution: (a) Identify primary growth factors substitutes (b) Test more cost-effective / stable alternatives, (c) Measure substitute functionality. The fourth solution is to develop a bioreactor platform or chemical solution to mitigate media toxicity.

Specific Aims (projects): Identify 3-4 specific aims to be achieved in a 5-year road map. Utilize a specific cell type or panel of primary cells to test the following:

Specific Aim 1: Characterize albumin/serum components to build a defined, universal basal medium

Specific Aim 2: Identify molecules that can be developed to replace the biological components in media for the majority of cell types (Determine the cells types – MSC, T cells)

Specific Aim 3: Build international consensus and harmonization on regulatory issues involving media components (a) Human component origins, (b) Testing (c) Shipment (d) Associated documentation (e) Labeling

Anticipated Outcomes:
1: A medium that can be used internationally for at least one cell type
2: A panel of cell lines that can be used for calibration
3: SOPS and protocols that will accelerate media development
4: IP and knowhow
5: CE Mark, 510K, licensable media
6: A synthetic serum substitute
7: Tests to qualify albumin or serum substitutes

Project Milestones- Media	**Lead**	**Anticipated Outcome**
1. characterize albumin / serum components to build a defined, universal basal medium		
2. Identify molecules that can be developed to replace the biological components in media for the majority of cell types		
3. Build international consensus and harmonization on regulatory issues involving media components (a) Human component origins, (b) Testing, (c) Shipment, (d) Associated documentation, (e) Labeling		
4.		
5.		

Manufacturing Impact Topics (MITs): Bioreactors

Problem: There are numerous problems facing the advancement of bioreactor technology for regenerative medicine. Some of these problems include: (1) Adherent cells in bioreactors (2) Cost, sterilization, space (3) Scale, small size bioreactors not available (4) Front end costs (5) Sensors and visualization (6) Microenvironment can be different in various parts of a bioreactor, microenvironment control (7) Sampling (8) Sterility (9) Multistep process adaptability (10) Downstream processing, initial primary harvest, separation from matrix (11) Initial upstream processing (12) Limited bioreactor design for tissue products, 3D and personalized medicine (13) Adaptability for bioreactors (14) Media design for scale, feed strategies (15) Gene modification at scale, modify and expand, expand and modify (16) Cell selection, sorting, hi speed sorting (17) Harvest cells in a non-destructive way.

Solution: There were 6 solutions that we identified at our second Industry focus meeting where 3 companies (Cord Blood Registry, ThermoFisher, Pfizer) formed a break out group to develop these solutions that would be achieved over a 5 year period. These solutions included (1) Developing in process testing, in-line, at-line, in-process testing – resources and access to technologies in academics and industry, (2) Redesign for 2D, 3D and personalized medicine closed system manufacturing (3) Large scale in-line gene modification (4) Adapt cells to suspension, (5) understanding the biology of adaptation or organoid culture (6) Universal cell

Specific Aims: Identify 3-4 specific aims to be achieved in a 5-year road map.

Specific Aim 1: Develop in line testing to identify key parameters to monitor, cell health, visualization of cells, sentinel systems, sterility, endotoxin, mycoplasma

Specific Aim 2: Understand the biology of adaptation for suspension culture, organoid or aggregate culture – choose one cell type

Specific Aim 3: Harvest cells in a non-destructive way, acoustic focusing for cells, tissue sheets, tubes

Specific Aim 4: Universal/synthetic cells

Anticipated Outcomes:
Enabling technologies will result that can be used to further the development of cell based and tissue engineered technologies.

Project Milestones- Bioreactors	Lead	Anticipated Outcome
1. Develop in line testing to identify key parameters to monitor, cell health, visualization of cells, sentinel systems, sterility, endotoxin, mycoplasma		
2. Understand the biology of		

adaptation for suspension culture, organoid or aggregate culture – choose one cell type		
3. Harvest cells in a non-destructive way, acoustic focusing for cells, tissue sheets, tubes		
4. Universal/synthetic cells		
5.		

Manufacturing Impact Topics (MITs): Preservation

Problem: Preservation and storage of cells is currently restricted to cryogenic temperatures, which limits time at ambient temperatures, handling procedures, logistics, cost, efficacy, safety, equipment requirements, retrieval and other adverse impacts to the product. Development of practical non-cryogenic storage methods would simplify point of care and would also ease shipment (size) and cost of validation.

Solution: There were four main solutions identified at our second Industry focus meeting where 4 companies (ThermoFisher, Janssen, AABB, Fluidigm) formed a break-out group to develop potential solutions that could be achieved within a 5-year period. The first proposed solution was stabilizer development. The second solution was to develop a customized distribution channel. The third solution was to foster training and build infrastructure at point of care. The final solution was to implement ambient storage at the user or intermediate site with front-end cryogenic storage at distribution centers or longer term storage.

Specific Aims: Identify 3-4 specific aims to be achieved in a 5-year road map.
Specific Aim 1: Develop potential stabilizers that will allow storage and distribution at higher than cryogenic temperatures. (a) Investigate and develop effective stabilizer formulation compositions (DMSO free and trehalose as examples), (b) Investigate and develop effective lyophilization formulations, preferable using GRAS reagents and including formulations for reconstitution (c) Characterize the effect on the product (cellular function) and perform generalproduct development - tests, specifications, duration, temperatures both pre- and post-thaw, (d) investigate the feasibility of novel drying technologies; magnetic fields, etc.
Specific Aim 2: Customized distribution channel and packaging. (a) Size and handling – both shipping cost and convenience for end user, (b) Cost of goods – custom, validated shippers
Specific Aim 3: Foster training and build infrastructure at point of care, including both personnel and equipment at sites.
Specific Aim 4: Develop protocols for non-cryogenic end user storage with front-end cryogenic storage. This will involve consideration of (a) Short-term ambient storage (<30 days) with front-end cryogenic storage, (b) Tissues as well as cells, and (c) Exploration of other temperatures (including other frozen temperatures or refrigeration) that are more commonly and easily implemented.

Anticipated Outcomes:
(1) Hybrid storage that enables centralized cryogenic with non- cryogenic distribution. Characterize range of viable temperatures and time limits – defined temperature/time ranges for various product types that will enable higher temperatures to be used for end delivery directly to the patient.
(2) Drying technologies. Determine the feasibility of various drying technologies (processes and formulations) and recovery solutions for various product types
(3) Device/Packaging. Define and design of device/packaging to maintain product in a closed system that will maintain viability and efficacy through delivery to patient
(4) Improved stabilizers that will protect cells at higher temperatures or extend handling times during processing

Project Milestones- Preservation	**Lead**	**Anticipated Outcome**
1. Develop potential stabilizers that will allow storage and distribution at higher than cryogenic temperatures.		
2. Customized distribution channel and packaging.		
3. Foster training and build infrastructure at point of care, including both personnel and equipment at sites.		
4. Develop protocols for non-cryogenic end user storage with front-end cryogenic storage.		
5.		

Manufacturing Impact Topics (MITs): Large Scale Manufacturing

Problem: The field currently does not have a fully integrated module from needle to needle that offers a closed-customized system that can manufacture tissue engineered and regenerative medicine based products from tissue acquisition all the way to final product that is ready for a patient. However, in the field, we witness the presence of solutions for specific areas (such a manufacturing (Bioreactor based), Thawing, Cryopreservation etc..) and an effort to connect these solutions are essential. Real world data is lacking that can provide the benefits such a closed system can offer for rapid regulatory approval of ground-breaking allogeneic therapies. There are additional challenges associated with autologous treatments such as the high cost of goods. There is also the requirement for available clean room space for autologous treatments and developing a process that is space efficient. A process also needs to be developed to deliver the treatment back to the patient (autologous). Also, will autologous processes be centralized or done at different point of care sites. There also currently is no viable business model. Analytical challenges remain for efficient, cost-effective release for autologous treatments. There is also a lack of available standards, such as tubing sizes.

Solution: The solution to this problem is to engineer a fully integrated module that offers a closed-customized system that can manufacture tissue engineered and regenerative medicine based products for large scale (Allogeneic and Autologous therapies). At our second Industry Focus meeting we had two breakout groups (A) 5 companies (Pfizer, GE Healthcare, Celgene Cellular Therapeutics, Panasonic Healthcare, and Lonza) and (B) 6 companies (Lonza, Materialise, Panasonic Healthcare, Janssen, ThermoFisher, EMD Millipore) which collectively provided solutions to these current challenges. Solutions included: (1) Develop standard processes (harvest, process, deliver) or be able to develop a robust process for autologous treatments that can be performed locally (proximal to the patient); (2) Increase awareness and develop processes that use custom, closed cassettes for process and link parts of the process together; (3) Allogeneic = centralized location for processing; autologous = individual site locations; (4) Show that process can be developed at reasonable cost; (5) Rapid batch testing – define cost and time details.

Specific Aims: Identify 3-6 specific aims to be achieved in a 5-year road map.

Specific Aim 1: Delivery of substrate into the automated processing module. This would be achieved by building on apheresis systems to make easily adaptable to system. How to address difficult tissues (i.e. solid tissues like placenta)? We would bring tissues to the stage of apheresis.

Specific Aim 2: Development/refining of an automated module to make "cells." By using and integrating the current available technologies (ex: bioreactor based) and potentially advance these solutions to next level such a continuous cell based manufacturing. The integration in terms of IT/Data is also a key component of this solution.

Specific Aim 3: Improvement of Unit Ops to be more reproducible (increased robustness) Increased analytics/in process controls and adjust on the fly. Better in process analytics to improve robustness and control (for the modular process, which needs to be defined).

Specific Aim 4: Rapid batch testing – define cost and time details

Specific Aim 5: Standardized disposable connectors and process materials

Specific Aim 6: Increase awareness of disposable technologies and help with adoption in trials

Anticipated Outcomes: The development of such a fully integrated module for a closed-customized manufacturing system for tissue engineered and regenerative medicine based products would provide the following anticipated outcomes: (1) development of off the shelf modular system, (2) development of modular units to facilitate manufacturing process for allogeneic therapies, and (3) development of an intelligent system that interfaces with different modules along a manufacturing process. There would also be additional benefits to numerous participating companies that could assist with developing different modules to plug and play into this fully integrated module. For instance, a plug and play module for cell expansion or a plug and play module for 3D bioprinting. Additional areas of synergy include testing out defined serum for different cellular products or developing in process controls and analytics to monitor and optimize manufacturing processes. Additional anticipated outcomes include: (4) Development of entire autologous treatment process that can be entirely performed proximal to the patient (in the same center) and (5) Identify standards and suppliers that provide cross-compatible process materials.

Project Milestones- Manufacturing	**Lead**	**Anticipated Outcome**
1. Delivery of substrate into the automated processing module.		
2. Development/refining of an automated module to make "cells."		
3. Improvement of Unit Ops to be more reproducible (increased robustness) Increased analytics/in process controls and adjust on the fly.		
4. Rapid batch testing		
5. Standardized disposable connectors and process materials		
6. Increase awareness of disposable technologies and help with adoption in trials		

Manufacturing Impact Topics (MITs): Quality Control

Problem: There are different problems whether organ or cells which can include (1) loss of product (both organs and cells) including for solid organs having to grow two organs for testing, precious starting materials for testing, and in 10% of cells lost at each step of testing; (2) sterility of end product after testing (both organs and cells). There are also problems before, during, and at product end. Decisions need to be made as far as what testing needs to be done at each step. In addition testing the media is not sufficient for QC of the organ. What needs to be QCed includes viral, media, organ, cell and scaffolds. Deciding on the best testing methods is also a challenge which could include imaging, characterization, molecular, and chemical analytical methods. Another challenge that frequently comes up is that testing a portion of the product may not represent the entire product. There are also challenges around qualified sensors and endotoxins.

Solution: There were 7 main solutions that we identified at our second Industry focus meeting where 8 companies (BD Technologies, Akron, AABB, Integra LifeSciences, ACell, GE Healthcare, Celgene Cellular Therapeutis, and Fluidigm) formed a break out group to develop solutions that would be achieved over a 5 year period. These solutions included (1) Develop inline sensors in bioreactors so that the whole culture is not contaminated during testing; (2) Develop a technology that could be applicable to all; (3) Sensor that applies to adherent cells; (4) Sensor that applies to adherent cells or tissue; (5) Standardize media testing including sterility and measure all processes (carriers, no carriers); (6) Viability testing that is predictive of "true" cell viability; (7) Sample aliquots for single cell genomic analysis.

Specific Aims: Identify 3-4 specific aims to be achieved in a 5-year road map.

Specific Aim 1: Develop a multiplex biological profile system for a single sample in real time (ie microfluidics) (a) Viability, (b) Cytokines, (c) Cell surface markers, (d) Cell number, (e) Metabolites

Specific Aim 2: Develop a test for sterility that takes less than 48 hours. (a) Measure throughout the process (b) Molecular , (c) Quantifiable

Specific Aim 3: Expansion of imaging technologies for QC testing (a) Scaffolds, (b) Organ, (c) Index refraction for cell viability, (d) Cell scatter in flow cytometry for viability

Specific Aim 4: Incorporate single cell analysis (e.g. genomic profiles) into QC testing for accessing cellular phenotypes

Anticipated Outcomes:
(1) Be able to measure all components in real time (Viability measurements to measure damage along the way)
(2) Improve time of release of product in a safe and efficient manner
(3) Imaging technology would allow each organ to be verified and improve consistency
(4) Develop analysis tools to optimize cellular phenotypes for therapeutic applications

Project Milestones- QC	Lead	Anticipated Outcome
1. Develop a multiplex biological profile		

system for a single sample in real time (ie microfluidics) (a) Viability, (b) Cytokines, (c) Cell surface markers, (d) Cell number, (e) Metabolites		
2. Develop a test for sterility that takes less than 48 hours. (a) Measure throughout the process (b) Molecular , (c) Quantifiable		
3. Expansion of imaging technologies for QC testing (a) Scaffolds, (b) Organ, (c) Index refraction for cell viability, (d) Cell scatter in flow cytometry for viability		
4. Incorporate single cell analysis (e.g. genomic profiles) into QC testing for accessing cellular phenotypes		
5.		

Breakout Groups

Below are suggested breakout groups for each of the manufacturing impact topics (MITs).

Media	Bioreactors	Preservation	Manufacturing	QC