Reference Materials for Cell-based Medicinal Products: An Industry Perspective

Christopher A Bravery

cbravery@advbiols.com

Consulting on Advanced Biologicals

Overview

- Product RM
  - Patient-specific (mostly autologous) Products
  - Off-the-shelf (allogeneic Products)
  - Hypothetical case study example.
- Other RM
- Conclusions

Consulting on Advanced Biologicals

Patient-specific Products
General Issues

- Manufacturing scale is small
  - Batch-size often only a single unit.
- Each batch is made from a different source of starting material (donor), so highly variable
- It may not be possible/easy to get larger amounts of donor material or normal donor material (donor consent/national laws)
- Pooling multiple batches is likely to be prohibitively expensive and practically difficult to produce enough batches.
  - Unit scale means high COGs per unit
  - Time, facility and personnel capacity

Patient-specific Products
Possible Solutions (Ideas)

- Use a 'model' cell line
  - May require cloning of cell line to ensure consistency
  - Products often heterogeneous and poorly defined
- Rely on non-product RM's and regular process qualification
  - Ensure all analytical methods have alternative appropriate RM
- Donor (starting material) RM – '*the product is the process*'
  - Run a donor RM frequently and check the process is performing consistently
  - Requires methods to have adequate RM too (*see above*)
  - Doesn't solve problem of analytical methods RM's

Note: I know of no examples of developers trying any of these ideas.

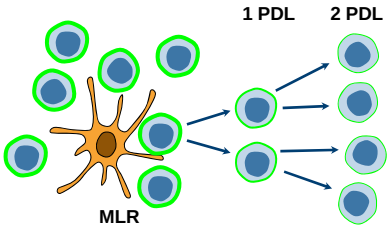
Off-the-shelf Products
General Issues

- Manufacturing scale is still generally relatively small
  - Batch-size 10's - 100's units.
- Cell banks often of limited size (e.g. lasting 2-4 years)
  - Need to manage high use of product RM with need to change MCB and RM from time to time.
  - Emphasis on need for the product RM
- Pooling multiple batches should be possible where a single batch is relatively small.
  - Potentially still expensive relative to biotech with probable greater use (more smaller batches)

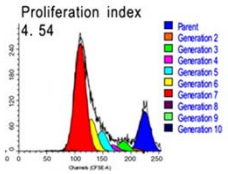
Hypothetical Case Study
Curzall™ (curicytes)

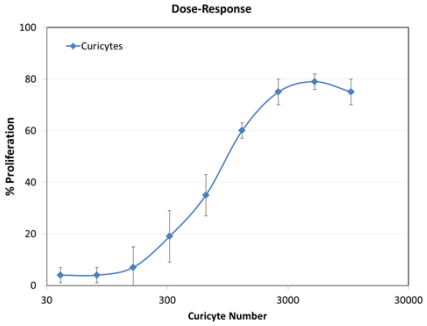
- Hypothetical product (based on real experiences)
- Case: Curzall™ is an immunotherapy product composed of a suspension of curicytes
  - Both autologous and allogeneic situations will be discussed
- Curicytes are APC's that stimulate an anti-tumour response (i.e. present known tumour Ag's).
- Since one of the critical uses of the product RM is to calibrate the potency assay (where no Intl RS exists) the following case study will explore the issues that arise when a product RM cannot be prepared.
  - Assumes the potency assay is quantitative and that the quantitation means something – this may not be the case.

Hypothetical Case Study
Curzall™ Potency Assay



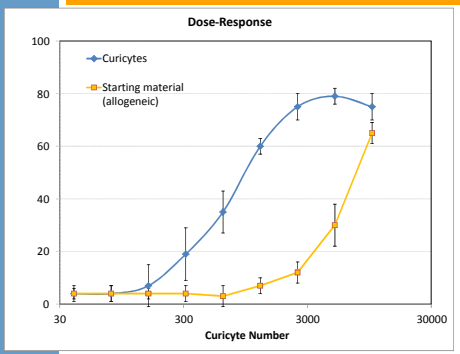
MLR
CSFE-labelled responders (lymphocytes)
+
Curicytes (DC's)





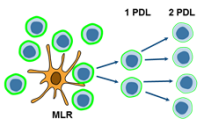
Note: This assay merely shows the curicytes are capable of stimulating an immune response, it is otherwise not specific for tumour antigens

Hypothetical Case Study
Reference Materials: Allogeneic

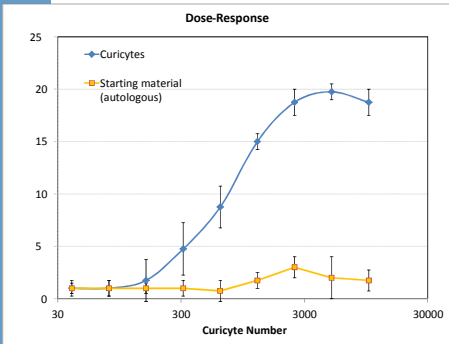


- Allogeneic curicytes; response primarily to allo-Ag's
- Different responders will give different responses
- ***Possible RM***
  - Curicyte 'product RM' plus a 'Standard responder' e.g. primary cells, cell line, or perhaps Ag-specific T cell clone/s.

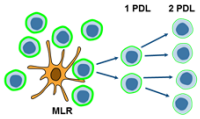
MLR
allogeneic responders (lymphocytes)
+
Allogeneic Curicytes (DC's)



Hypothetical Case Study
Reference Materials: Autologous



MLR
autologous responders (lymphocytes)
+
Autologous Curicytes (DC's)



- Autologous curicytes
  - response (presumably) primarily to tumour Ag's
- Different responders will give different responses
- ***RM issues***:
  - Can't pool batches of product (allogeneic to each other)
  - Possibly make large batch from single donor, but would also need same donor as responder.
  - Allogeneic responder = large batch variation/loss specificity.

Hard to think of a suitable RM

CAB

Consulting on Advanced Biologicals

Other Reference Materials
Flow Cytometry

- General RM for device
  - Calibration beads for fluorescent intensity measurement
    - Bead fluorescent standards to calibrate detectors
- Measuring changes in receptor density e.g. up-regulation of receptor over time in assay
  - Beads coated in known amounts of antibody to calibrate fluorescent intensity of labelled mAbs (fluorescence/mg protein) as well as number of mAb's binding per cell.
  - Product RM (if possible)

Or possibly

- Standard 'model' cell that responds in assay the same way as product (reliably, and can be banked)

CAB

Consulting on Advanced Biologicals

Other Reference Materials
Cytokine release

- Assays that measure release of cytokine, chemokine, growth factors etc.
  - Typically ELISA and related assays
  - In most cases an international RS or other standard for the cytokine will be available.
  - However, cytokine standard only controls for the bioassay read-out system (e.g. ELISA part)
  - The bioassay itself needs a RM to control for assay conditions
    - Product RM if possible

  or possibly
    - Standard 'model' cell that responds in assay the same way as product (reliably, and can be banked)
  - *Note: ELISA-type assays do not confirm the cytokine is itself active*
    - *May need confirmation (during development) by bioassay*.

CAB Consulting on Advanced Biologicals

Conclusions

- Preparation of a product RM for CBMP poses a number of issues
  - Difficult for off-the-shelf
  - Potentially insurmountable for patient-specific products
- The use of other RM's can compensate to some degree
  - Hard to think of alternatives for bioassays (e.g. potency)

CAB Consulting on Advanced Biologicals