

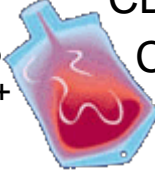
Comparability and Scale-up Challenges: Cell and Tissue Therapy Products

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Advanced Cell & Gene Therapy

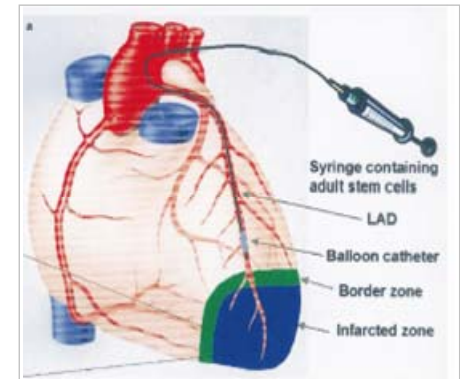
“Not Well-Characterized” Products

- Living cells **are** the product
- Heterogeneous composition
 - Known and unknown cell subpopulations, even if highly purified
 - Intrinsic biological variability
- Full product definition likely unattainable
- Product definition, process, testing evolve through trials
 - What is the relevant biological function?
How to measure function?
 - Which cells mediate the effect?

>99%
CD34⁺
Cells



CD33⁺, CD33⁻
CD38⁺, CD38⁻
CDX⁺, CDX⁻



Biological function?
Direct/indirect repair?
Humoral factors?
In vitro correlates for
in vivo function?

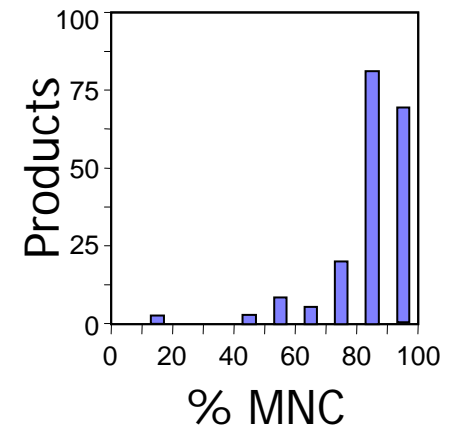
Strategies for Cell and Gene Therapy

- Cell therapy products cannot be fully characterized, *and* manufacturing changes are inevitable
 - Reagents, methods, process steps, manufacturing sites...
- Therefore, emphasize product characterization, process control
 - Controlled, consistent processes yield controlled, consistent products
 - Product characterization data supports comparability across process changes - PQ studies

Build Characterization Data Foundation

- Establish patterns for purity/identity data, functional testing
 - Cell-surface marker expression, humoral factor production, functional assays
- Assess consistency
 - Product to product, lot to lot
- Evaluate biological variability
 - Raw material, product
- Identify controllable sources of variability

**Cytapheresis Product
MNC Content**



Comparability - Bridging the Changes

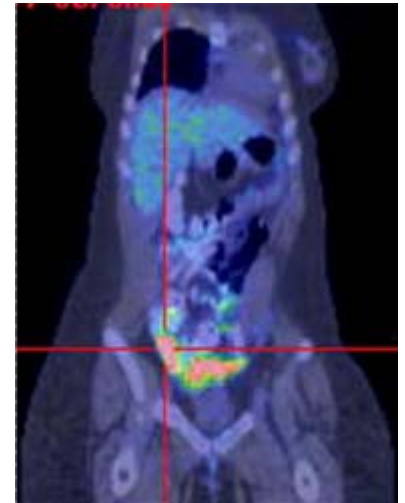
- Evaluate effect of process changes on product characteristics
 - *In vitro* testing - safety, identity/purity, potency
 - Look for differences in the *pattern* of purity/identity test results
 - Preclinical animal studies, clinical bridging studies as needed
- Detailed, written comparability protocol

Comparability Studies

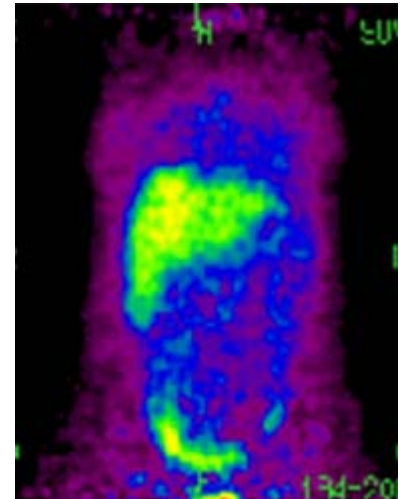
- Product characterization
 - Cell population(s) correlating with efficacy - difficult challenge
 - Other product components
 - Cell subpopulations, residual process reagents
- Develop and qualify/validate analytical methods
 - For lot release, for additional characterization
 - Develop understanding of analytical limitations
 - May need novel methods to detect changes in product

In Vivo Cell Distribution

- Imaging technology for cell tracking
 - Isotopic imaging - PET-CT, SPECT
 - Fluorescence, magnetic particle imaging
- Comparability, development tool
 - Bridge manufacturing changes
 - Fresh vs. frozen/thawed cells
 - Serum vs. serum-free
 - Animal model qualification
 - Clues to biological function



Pre-Rx PET



FDG-labelled MAK cells
t = 3 hr., PET-CT