Human Platelet Lysate requirements for cell therapy expansion in support of clinical trials

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The Issue

- cGMP manufacture of cell therapies needs to avoid the use non-human animal supplements.
  - Current options:
    - Defined media
      - Limited utility to date
    - AB serum
      - Not optimal for culture of some cells
      - Supply concerns
    - Human platelet lysate (HpL)
      - Extensive literature demonstrating utility of HpL for cell culture
      - Multiple companies/organizations marketing or developing HpL product formulations
        - » There is variability in manufacture of HpL
        - » Establishing a minimum set of criteria for HpL production/ characterization is needed

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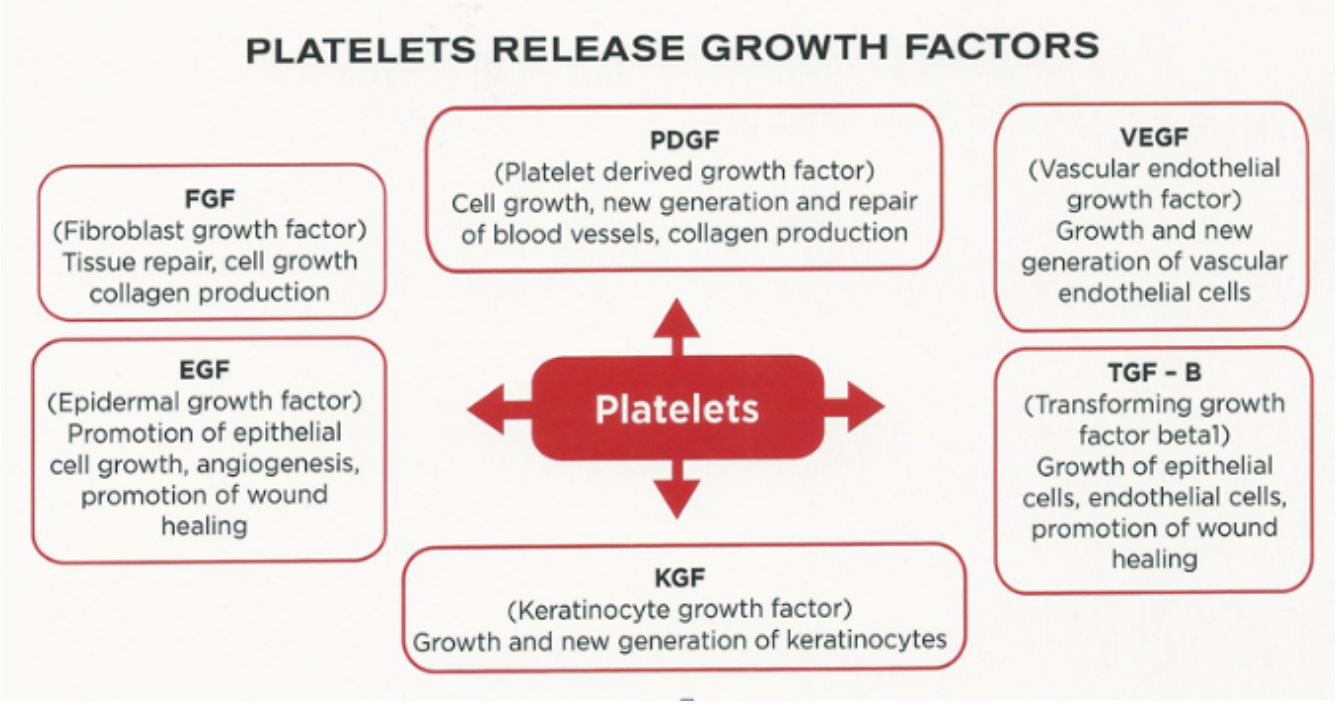
Why platelets?

- The growth factors contained within platelets are key factors for tissue repair and regeneration, vital to inducing cells to grow rapidly, but not abnormally in the body.



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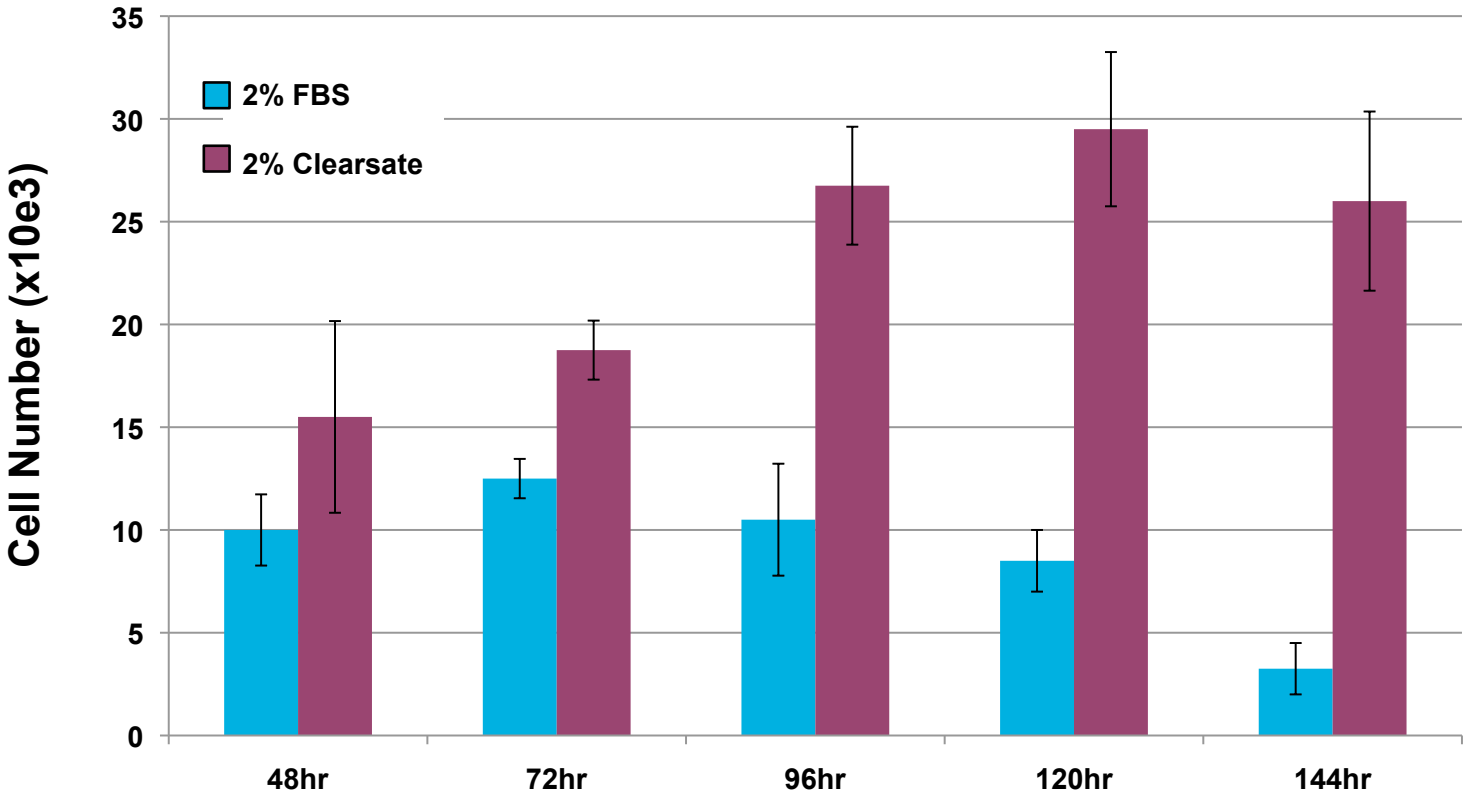
HpL VS FBS Effect On CB MSC Proliferation



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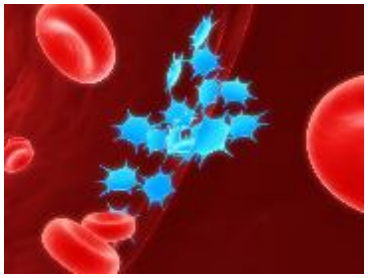
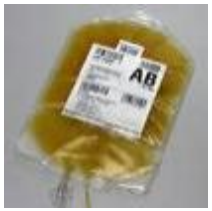
General Manufacturing Scheme for HpL

Platelets in peripheral blood



Platelets harvested



Platelets Washed

Platelets flash frozen

Platelets thawed, membranes rupture

Centrifugation

Multiple filtrations

Finished product

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HpL Starting Material

- Typically expired platelets collected for transfusion are used as starting material
  - Collected at accredited (AABB, FACT) facilities with that follow State and CFR guidelines for clinical blood products
    - The appropriate consent must be obtained from donors prior to collection and use
    - IDM and sterility tested prior to release for manufacture of HpL
    - Assures a consistent, safe, traceable starting material with QA/QC oversight
    - Need to finalize how “old” can expired platelets can be and still be acceptable for use

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HpL Production Process

- Standardization of policies and procedures for HpL manufacturing processes assure production of a safe, consistent HpL product
- Manufacturing processes should be cGMP compliant, with Quality oversight
  - Environment, equipment, personnel, manufacturing supplies
    - Monitoring, validation, training, qualification
- Implementing these practices for HpL production is a key support for cGMP manufacture of the final cell therapy product

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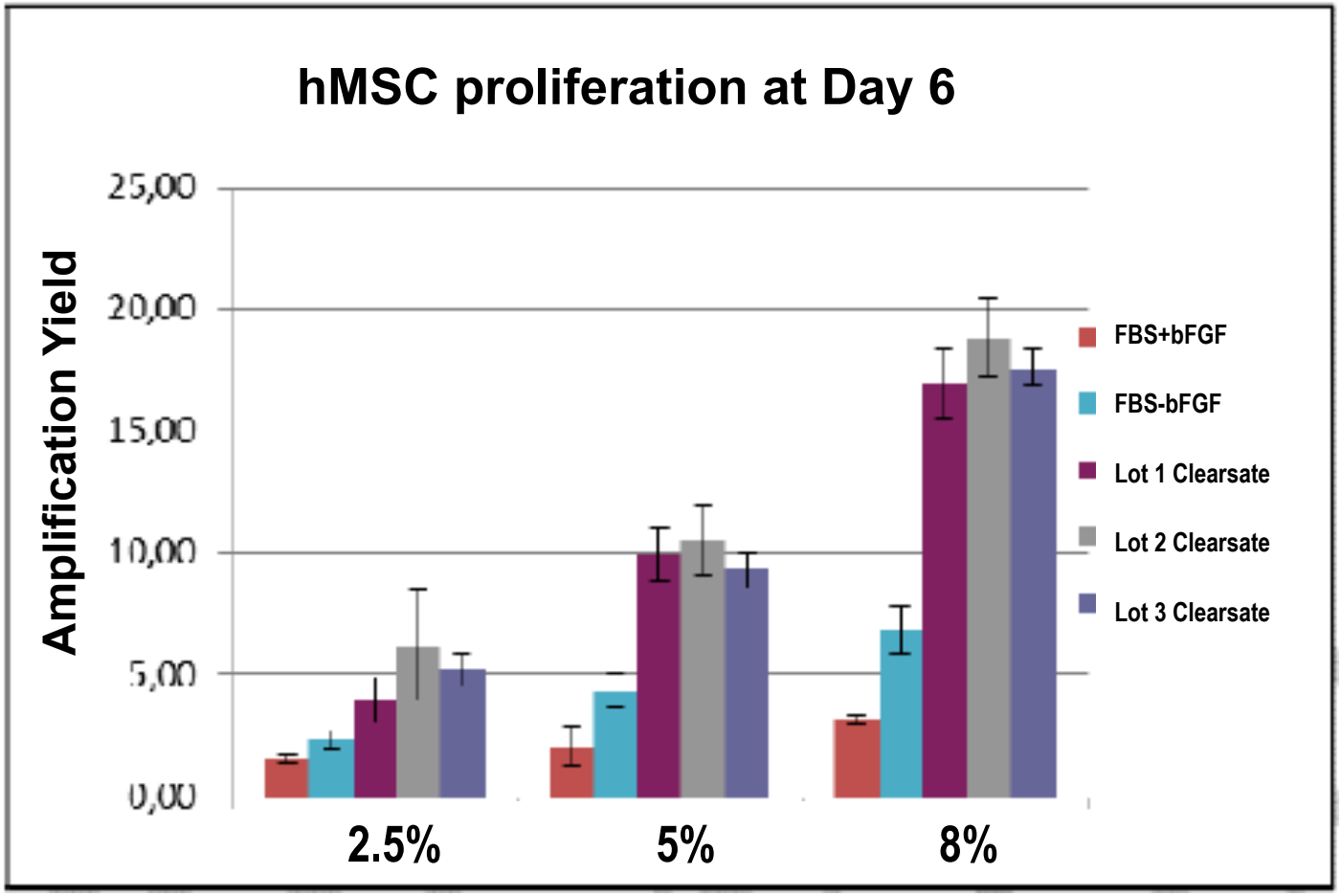
Lot to Lot Consistency Assessment



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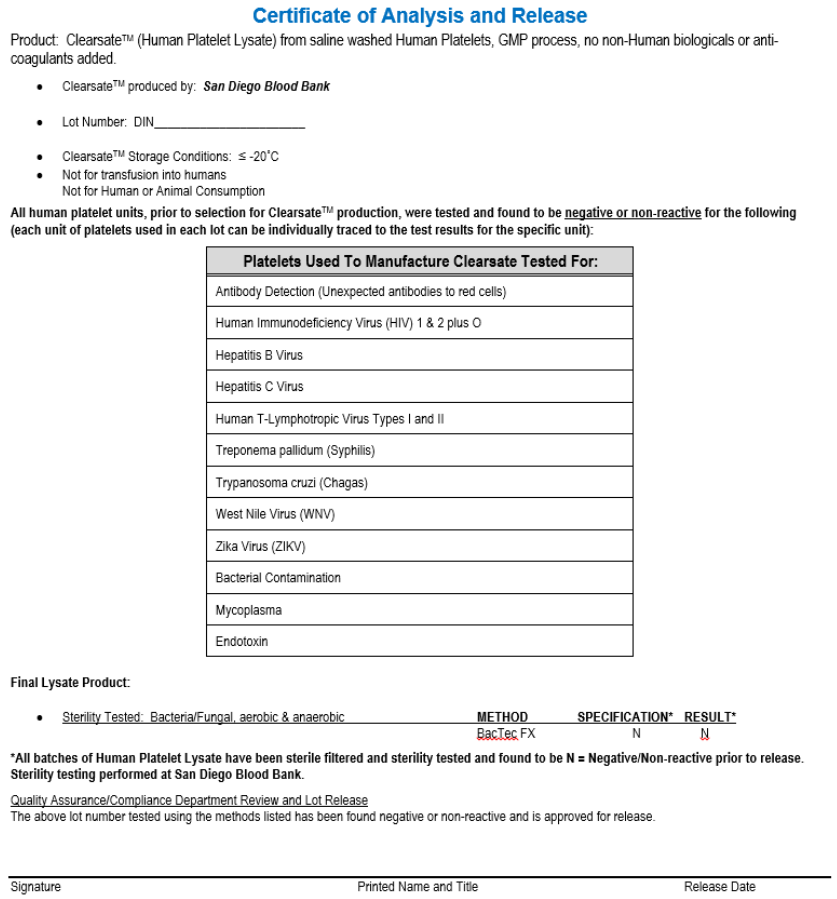
Product Characterization

- A Certificate of Analysis (CoA) should be included with each HpL manufacturing lot
  - Additives*
  - Lot number
  - Protein concentration
  - Endotoxin
  - IDM
  - Mycoplasma
  - Sterility
  - Expiration Date

*if used, for heparin, porcine source may be an issue



Certificate of Analysis and Release

Product: Clearsate™ (Human Platelet Lysate) from saline washed Human Platelets, GMP process, no non-Human biologicals or anti-coagulants added.

- Clearsate™ produced by: ***San Diego Blood Bank***
- Lot Number: DIN_____
- Clearsate™ Storage Conditions: ≤ -20°C
- Not for transfusion into humans
  Not for Human or Animal Consumption

All human platelet units, prior to selection for Clearsate™ production, were tested and found to be negative or non-reactive for the following (each unit of platelets used in each lot can be individually traced to the test results for the specific unit):

Platelets Used To Manufacture Clearsate Tested For:
Antibody Detection (Unexpected antibodies to red cells)
Human Immunodeficiency Virus (HIV) 1 & 2 plus O
Hepatitis B Virus
Hepatitis C Virus
Human T-Lymphotropic Virus Types I and II
Treponema pallidum (Syphilis)
Trypanosoma cruzi (Chagas)
West Nile Virus (WNV)
Zika Virus (ZIKV)
Bacterial Contamination
Mycoplasma
Endotoxin

Final Lysate Product:

	METHOD	SPECIFICATION*	RESULT*
• Sterility Tested: Bacteria/Fungal, aerobic & anaerobic	BacTec FX	N	N

***All batches of Human Platelet Lysate have been sterile filtered and sterility tested and found to be N = Negative/Non-reactive prior to release. Sterility testing performed at San Diego Blood Bank.**

Quality Assurance/Compliance Department Review and Lot Release
The above lot number tested using the methods listed has been found negative or non-reactive and is approved for release.

Signature | Printed Name and Title | Release Date

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HpL Product Characterization

- Stability
  - A stability plan may be needed to determine shelf life of HpL products for a specific storage condition
    - -20 or -80 C storage conditions
  - Stability may be assessed with an in vitro cell proliferation potency assay
    - May need to use FBS standard or develop an HpL reference lot as comparator

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Potency Assessment

- Used to support stability studies
- Used for HpL lot release criteria
  - Potential cell types to be screened:
    - MSCs, HSCs, other
  - Cell counts taken at multiple time points
  - Data compared to a reference standard

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HpL Quality Control and Assurance

- QA/QC oversight is a key aspect of HpL production to support cGMP cell therapy manufacture
  - Release of expired platelets as starting material for HpL manufacturing
  - Manufacturing standardization to assure safety and lot-to-lot consistency of the product

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Suggestions for FDA to Consider

- A draft guidance for sourcing platelets that are the starting material for HpL production
  - Transfusion-grade Platelets sourced from cGMP facilities with appropriate accreditations, Consent and Quality oversight
    - Assures safety and consistency of starting material, typically expired platelet product and still acceptable for HpL manufacture
- A cGMP compliant HpL manufacturing process preferred with Quality program oversight supporting environmental, equipment, personnel and materials management
- A CoA with each manufacturing lot of HpL having the minimum criteria listed below:
  - Sterility, protein concentration, IDM, endotoxin, mycoplasma, lot number, expiration date, additives (if used)
  - Optional: Growth factor(s) content, potency assay results

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