Effective Dosage: A Pharmacokinetic Approach to Better Understand Pharmacodynamic Responses in Cardiac Cell Therapy Trials

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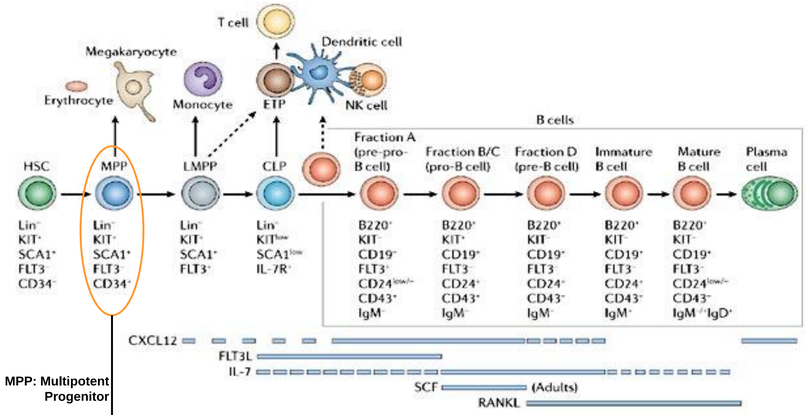
Background

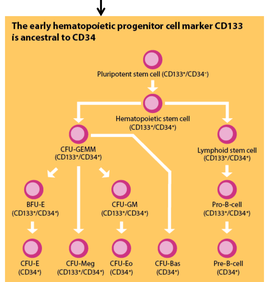
Different therapeutic strategies for autologous bone marrow derived cardiovascular cell therapies have reported mixed results with respect to patient benefit. It has been hypothesized that these differences in patient benefit could be due to the differences in effective dosage of certain cell types including CD34 positive and CD133 positive stem cells. Effective dosage varies according to the number of cells available in a patient sample for delivery multiplied by the efficiency of the delivery route. This is consistent with the Food and Drug Administration's guidance of regulating cardiovascular cell therapy products as combination products requiring a dedicated delivery system. Response to therapy (pharmacodynamics) may be better understood by tracking the effective dosage at a specified time post delivery (pharmacokinetics).

CD34⁺ Cells



MPP: Multipotent Progenitor

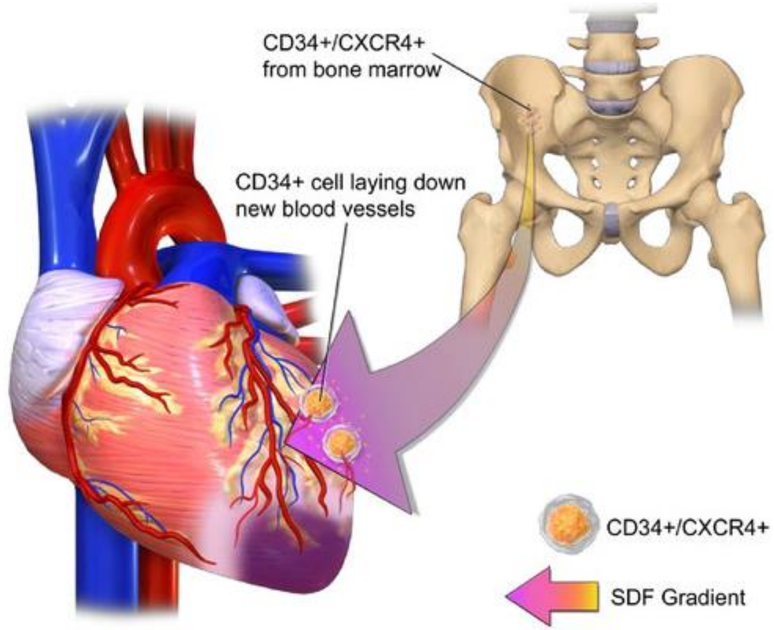
Nagasawa *Nature Reviews Immunology* 6, 107–116



https://www.miltenyibiotec.com/en/products-and-services/macs-cell-separation/cell-separation-reagents/hematopoietic-stem-cells.aspx

CD133 and CD34 are coexpressed on early hematopoietic progenitors with multipotent differentiation potential such as CFU-GEMM (colony forming units of granulocytes, erythrocytes, macrophages and megacaryocytes). CD34 is a well established hematopoietic stem and progenitor cell marker for human cells and can be found on late progenitors such as Pre-B cells, late erythroid progenitors and other more committed hematopoietic progenitors.

CD34+ Cells in Clinical Studies



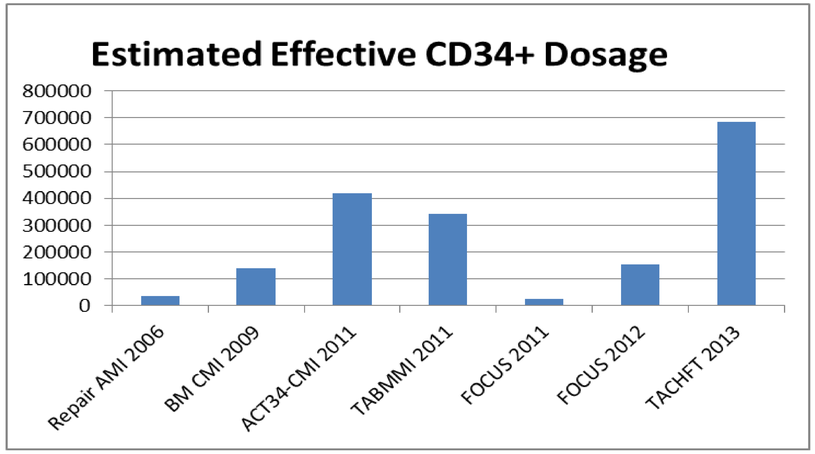
http://www.sec.gov/Archives/edgar/data/320017/000032001713000073/neosteminvestorpresentat.htm

A review of the published literature on bone marrow cell therapies in a setting of ischemic cardiovascular disease was performed to calculate the effective dosage of CD34+ cells. Effective CD34+ dosage was calculated using best estimates of efficiency of delivery, average cell counts, and average total cell dosage delivered. Efficiency of delivery at one hour was taken to be 1% for intracoronary artery delivery, 6% for straight needle intramyocardial delivery, and 18% for helical needle intramyocardial delivery based on published results and three cell retention studies performed by BioCardia and partners (see Retention Poster). Average reported CD34+ cell counts ranged from 1.5% to 100% and total cell dosage ranged from 7 million to 236 million cells.

Study	Total Cell Dose	%CD34 Reported	CD34 Counts	Estimated Retention (%)	Calculated Effective CD34+ Dosage
REPAIR AMI 2006[2]	236,000,000	1.5%*	3,540,000	1%	35,400
BM CMI 2009[3]	98,000,000	2.4%	2,352,000	6%	141,120
ACT34-CMI 2011[4]	7,000,000	100.0%	7,000,000	6%	420,000
TABMMI 2011[5]	100,000,000	1.9%	1,900,000	18%	342,000
FOCUS 2011[6]	30,000,000	1.5%	450,000	6%	27,000
FOCUS 2012[7]	100,000,000	2.6%	2,600,000	6%	156,000
TACHFT 2013[8]	200,000,000	1.9%	3,800,000	18%	684,000

*CD34⁺/CD45⁺ population reported

Estimated Effective Dosage



- Estimated effective dosage shows more than twenty five fold differences in average effective dosages of CD34+ cells in trials with bone marrow cell therapies for the treatment of ischemic cardiovascular disease.
- Effective dosage calculations show that studies that include non selected cells can have a greater effective CD34+ dosage than those in a recent CD34+ selected cell study.
- Global effective CD34+ dosage with high dose intracoronary artery administration can approach that of low dose intramyocardial administration, although it should be noted that there will be different regional distribution in the tissues.
- As endpoints are not standardized in these trials, in part due to different indications treated, outcome comparisons as a function of effective CD34+ cell dosage cannot be performed at this time.

Conclusions

Use of estimated effective dosage of delivered cells one hour after delivery may have value for future cell therapy study reporting. This approach is likely important for strategies using biomarkers for future clinical development.

References

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