COUNCIL MEETING
Sharing Our Passion for Life

Fine Tuning Collections: Tailoring the Collection to the Donor

Council Meeting 2016

Ken Friedman MD
Therapeutic Services, BloodCenter of Wisconsin
Milwaukee, Wisconsin

Study Collaborators

Sorelle Jefcik RN, Anand Padmanabhan MBBS, MA, PhD
Therapeutic Services, BloodCenter of Wisconsin
Milwaukee, Wisconsin

Disclosures

The following faculty and planning committee staff have no significant financial disclosures:

Name	Institution
Ken Friedman, MD	BloodCenter of Wisconsin
Sorelle Jefcik, RN	BloodCenter of Wisconsin

Disclosures

The following faculty and planning committee staff have the following financial disclosures:

Name	Institution	Disclosure
Anand Padmanabhan, MBBS MA PhD	BloodCenter of Wisconsin	Terumo BCT, Angiodynamics, Mallinckrodt Pharmaceuticals, Schlesinger Associates, LEK Consulting

Learning objectives

At the conclusion of this session, attendees will be able to:

- Determine what data are required in order to develop a predictive algorithm to determine the appropriate donor blood volume to process in order to meet a Transplant Center's CD34+ request
- Assess the quality of an implemented collection algorithm

Background

- An important source of stem cells for hematopoietic stem cell transplantation (HSCT) is peripheral blood (PB)
- Hematopoietic stem cells (HPCs) are collected for HCSTs using large volume leukapheresis (LVL) that involves processing typically ≥4 blood volumes to ensure adequate collection of HPCs

Background

- Large volume leukapheresis of NMDP donors is time-intensive, causes volume overload, hypocalcemia and platelet depletion.
- We performed a quality improvement study to generate a collection efficiency-based, data-driven algorithm for HPC collection to predict the required volume of donor blood to process in order to meet a CD34+ target.
- We then prospectively assessed the efficacy of the predictive model in NMDP donors

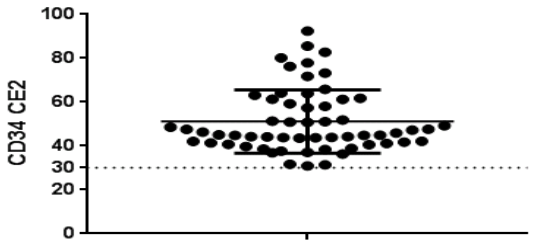
Methods

- HPC Collection procedure at BloodCenter of Wisconsin
  - Collection Device: Cobe Spectra
  - Anticoagulant: ACD-A/Heparin 11 unit/mL
    - Add 15 mL of ACD-A/Heparin solution to product bag
  - Single day collections are standard
    - Before predictive algorithm initiated
      - Donor blood processed: 24,000 mL
    - After predicted algorithm initiated
      - Pre-collection CD34 count is typically available within 3 hours of starting collection
      - Terminate collection when CD34 goal is estimated to be achieved

Methods

- We evaluated the CD34+ cellular collection efficiency 2 (CE2) in consecutive adult allogeneic (A-allo) collections (“training set”)

  CE2= CD34 cells collected/(BVP x precollection CD34 count)



# of Adult Allo Donors	Mean CE2 (1SD)
59	51 % (14%)

Methods

- Prediction of Blood Volume to be Processed (BVP) was calculated as follows:

$$BVP = \frac{\text{CD34 cell target}}{\text{CD34 CE2 x Precollection PB CD34 Count}}$$

BE THE MATCH COUNCIL MEETING: *Sharing Our Passion For Life*

Methods

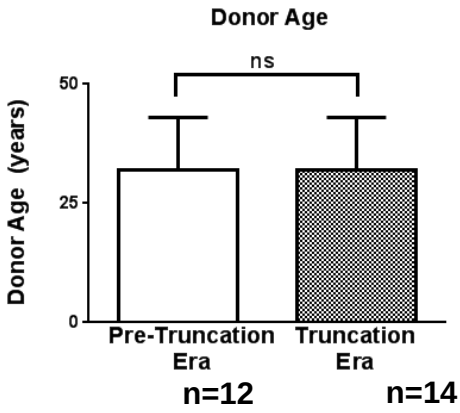
- In order to have a high level of confidence that the targeted dose of cells is collected, the CD34 CE2 in the prediction formula was set at:
- A-Allo- 30% (lowest CE2 attained in allo patients in the “training set”)

Results

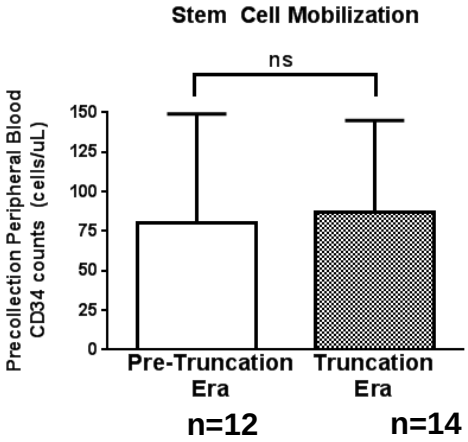
- Performance of the prediction formula was evaluated in HPC collections in NMDP donors over ~6 months

COUNCIL MEETING: *Sharing Our Passion For Life*

Truncation vs Pre Truncation Era:
Donor's age was similar



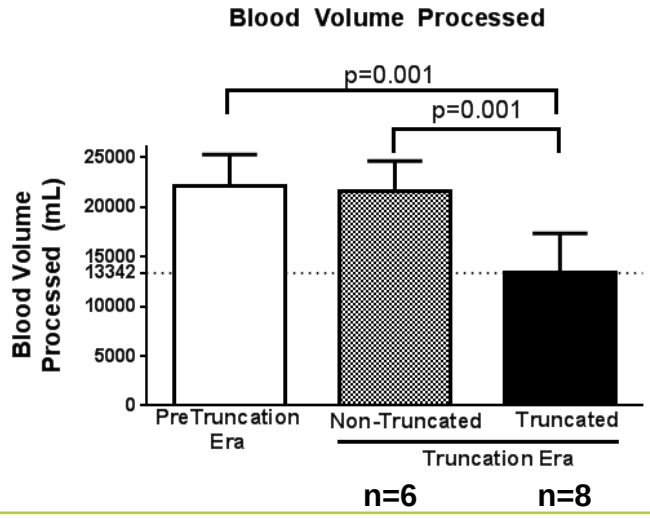
Truncation vs Pre Truncation Era:
Donors similarly mobilized



Results

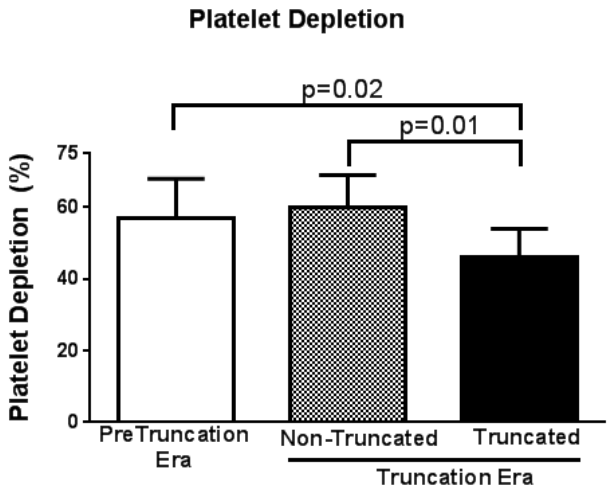
- 8 of 14 (57%) of procedures were truncated in the 6 month period

BVP: Significantly smaller in truncated procedures

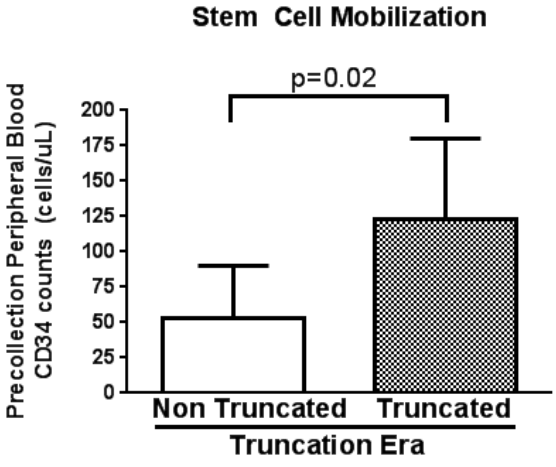


COUNCIL MEETING: *Sharing Our Passion For Life*

Significantly fewer platelets depleted in truncated procedures



High-mobilizing donors are more likely to be truncated



CD34 Yield

- All truncated collections resulted in adequate collection of CD34 cells (≥ target dose requested)

Conclusion

- More than 50% of procedures were truncated (8/14) using our prediction algorithm
- Lesser platelet depletion in truncated donors
- High mobilizing donors are more likely to have truncated procedures

Conclusion

- No prediction “failures” thus far
- Limited numbers. We are continuing to implement algorithm to ALL referred NMDP donors
- The blood volume processed for truncated procedures was significantly lower (~by 9L on average) compared to non-truncated procedures

Conclusion

- This approach may be particularly important in mitigating the risks of large volume leukaphersis (LVL), such as volume overload/citrate toxicity, while enhancing donor convenience and promoting optimal use of healthcare resources

Acknowledgments

BloodCenter of Wisconsin:
- Anand Padmanabhan
- Sorelle Jefcik
- Lori Eggert
- Patricia Fredrich
- BCW Apheresis RNs

Medical College of Wisconsin:
- Carolyn Keever-Taylor
- David Margolis
- Parameswaran Hari

NMDP and MCW:
- Volunteer PBSC donors

COUNCIL MEETING
Sharing Our Passion for Life

Mobilization and Apheresis in stem cell donors: Timing and Choosing the right apheresis platform

Council Meeting 2016

Jutta M. Rox* , Michael Punzel**, Johannes C. Fischer*

*Institute for Transplantation Diagnostics and Cell Therapeutics
Heinrich-Heine University Düsseldorf, Germany
**Former Cellex GmbH, Cologne

Disclosures

The following faculty and planning committee staff have the following financial disclosures:

Name	Institution	Disclosure
Johannes C Fischer, MD	ITZ at the University Hospital Düsseldorf	Received Grants from Chugai and Terumo BCT
Jutta M Rox, MD		
Michael Punzel, MD	Cellex/ before ITZ	

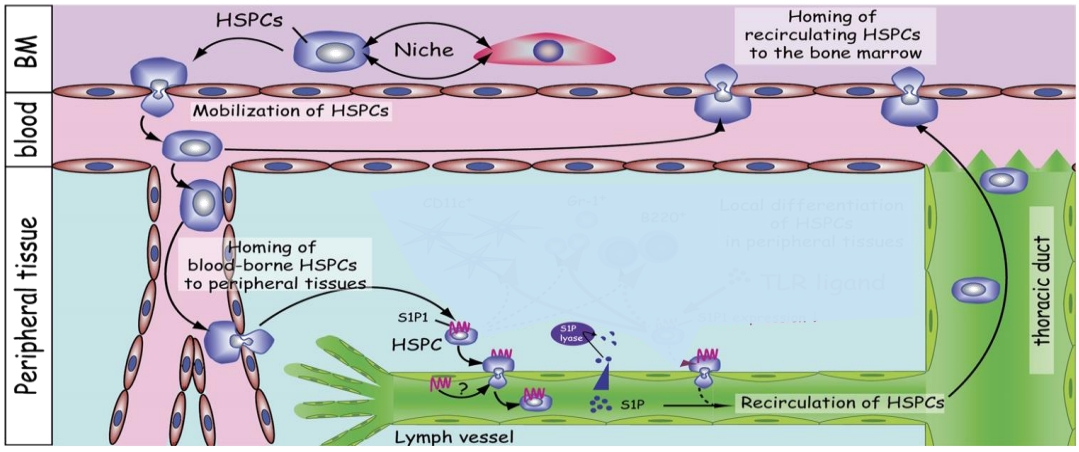
Learning objectives

At the conclusion of this session, attendees will be able to:

- Define Risk Factors for Poor Mobilizers
- Define best Apheresis Window through the Mobilization Course
- Know, which Apheresis Device/ Platform is Preferable in poor Mobilizers

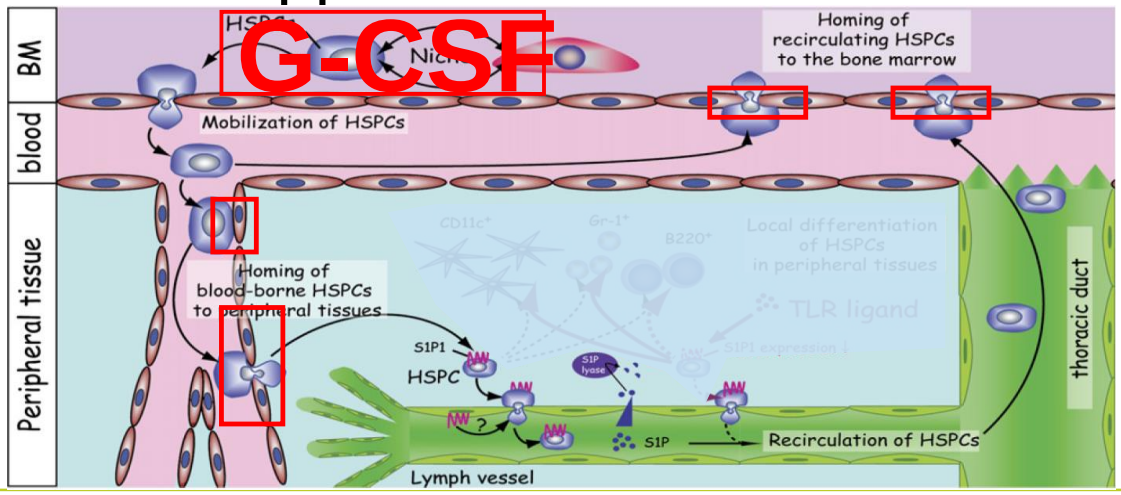
Why Mobilization

Hematopoietic Progenitor Circulation



Massberg et al, 2007 Cell 131, 994-1008

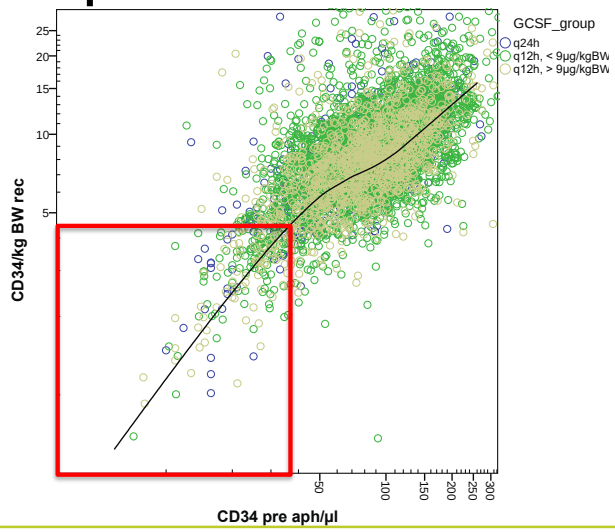
What happens due to G-CSF?

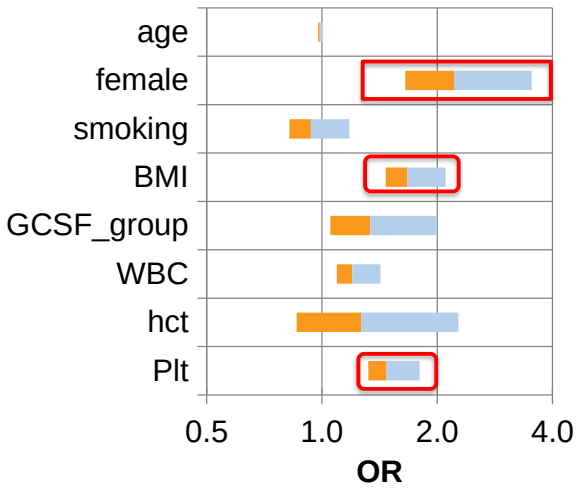


The Cellex DUS cohort

	1) q24h		vs 2	vs 3	2) q12h, < 9µg/kgBW		vs 3	3) q12h, > 9µg/kgBW		overall	
n	**593**				**3813**			**1285**		**5691**	
male	**398**	67,1%			**3037**	79,6%		**667**	51,9%	**4102**	72,1%
female	**195**	32,9%	< 0.01	< 0.01	**776**	20,4%	< 0.01	**618**	48,1%	**1589**	27,9%
MUD	**571**	96,3%			**3800**	99,7%		**1112**	86,5%	**5483**	96,3%
family	**22**	3,7%	< 0.01	< 0.01	**13**	0,3%	< 0.01	**173**	13,5%	**208**	3,7%
BW donor (SD)	**80,2**	15,1	< 0.01	< 0.01	**86,2**	15,6	< 0.01	**71,6**	14,2	**82,3**	16,4
range	49	145			53	160		47	170	47	170
age (SD)	**40,48**	8,683	< 0.01	< 0.01	**34,11**	9,88	< 0.01	**35,14**	11,779	**35,01**	10,4
range	19,61	66,73			18,84	63,26		18,44	73,886	18,44	73,89
BMI (SD)	**25,65**	3,892	< 0.01	< 0.01	**26,57**	4,188	< 0.01	**23,62**	3,7039	**25,81**	4,232
range	16,9	45,33			17,24	45,67		16,48	52,469	16,48	52,47
Smoker 0		72,4%	n.s.	n.s.		71,6%	n.s.		72,3%		71,8%
1-7		7,1%				9,1%			8,7%		8,8%
8-20		15,4%				17,7%			18,0%		17,5%
>20		5,1%				1,6%			1,0%		1,8%
G-CCSF	**10,83**	0,82	< 0.01	< 0.01	**8,383**	0,405	< 0.01	**9,521**	0,6359 15,61052 631pro57	**8,873**	0,961
range	6,943	15,96			4,574	8,991		9,013 894		4,574	15,96
rec weight	**73,1**	21,77	< 0.01	n.s.	**76,49**	21,26	< 0.02	**74,86**	20,22	**75,77**	21,11
range	7,5	160			4	206		2	187,5	2	206
CD34 pre	**87,81**	46,91	< 0.01	n.s.	**98,21**	49,04	< 0.01	**89,88**	50,823	**95,26**	49,41
range	10	272			3,46	372		7,88	480	3,46	480

Apheresis Yield

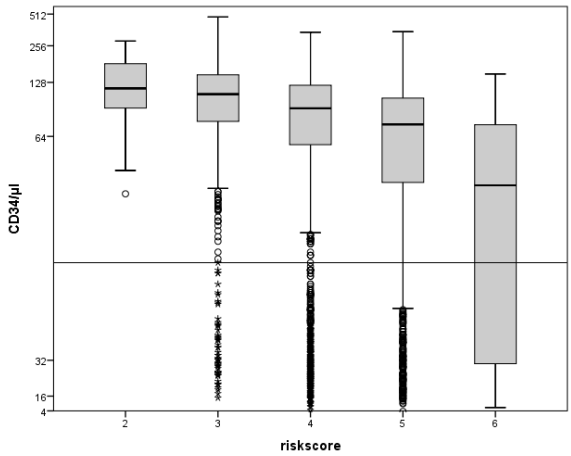




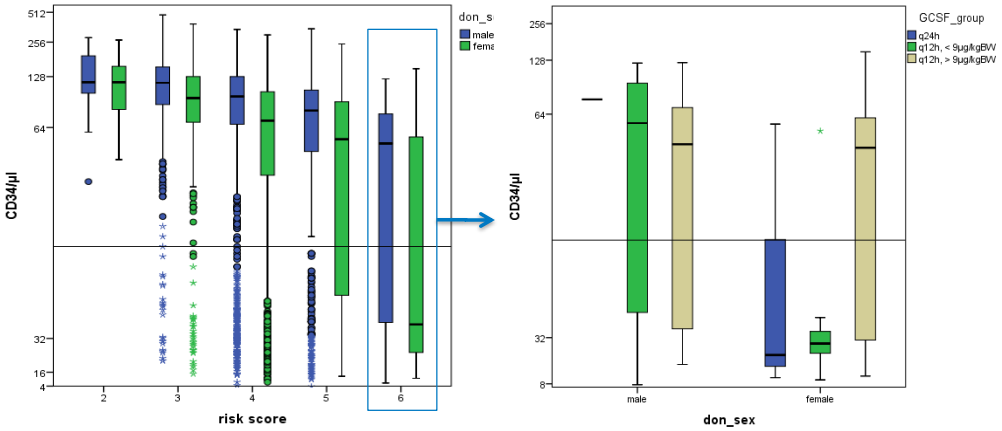
Risk Score for low Mobilizer

BMI	PLT >290		PLT 170-290		PLT <170
>34,5	**134** +/-60,3 n=60	< 0.013	**115** +/-45,6 n=144	< 0.015	**91,6** +/-44,1 n=28
	< 0.01		< 0.001		ns
20,7-34,5	**114,2** +/-57,5 n=902	< 0.001	**94,8** +/-46,6 n=3291	< 0.001	**81,8** +/-42,4 n=727
	< 0.001		< 0.001		<0.001
<20,7	**89,2** +/-51,6 n=103	< 0.001	**70,4** +/-39,4 n=288	<0.001	**52,6** +/-30,3 n=76

2	3	4
3	4	5
4	5	6



Male/ Females; G-CSF dosing



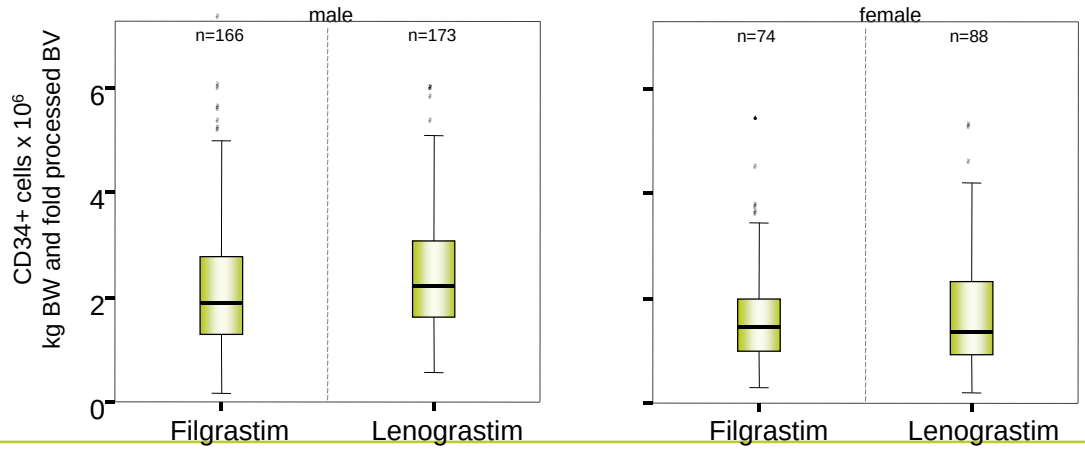
Higher doses of G-CSF may rescue in females but not in males

Split dose is favorable

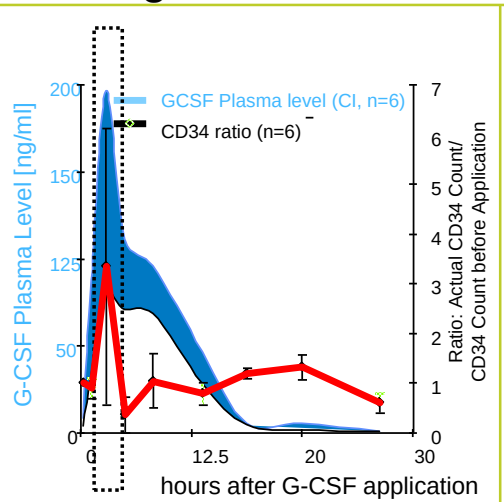
Risk Factors for Poor Mobilization

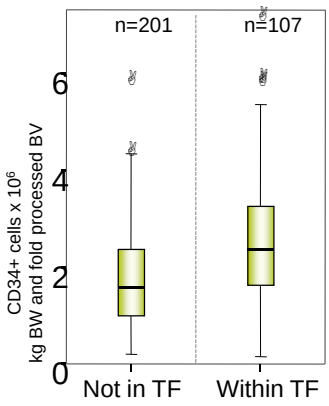
- Low BMI index
- Low pre Mobilization Plt Count
- Female Donors
- G-CSF q24h instead of G-CSF q12h
- (G-CSF dose)

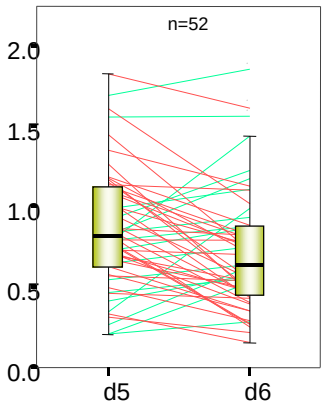
G-CSF- Mobilization Filgrastim vs. Lenograstim; a Phase III comparison in allogeneic donors.(Fischer et al. BJH 2004)



Timing of last G-CSF influences Apheresis result





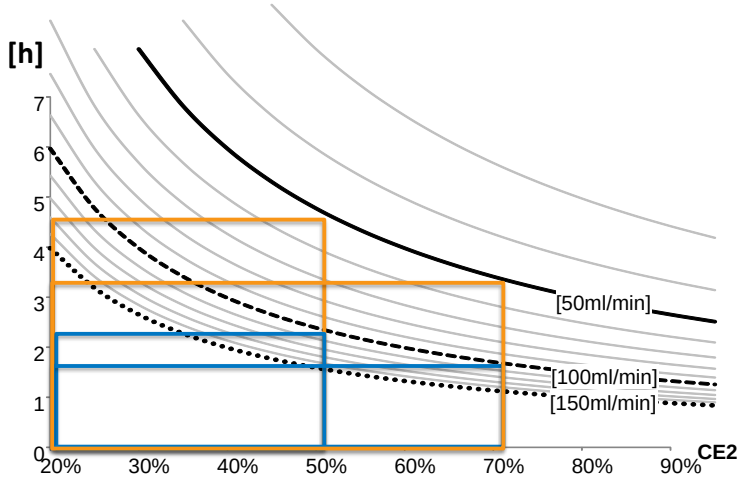


Collection Window within the Mobilization Course

- 2-6h after last G-CSF on d5
- d5 better than d6

Apheresis Time Calculation

Target [10^6]	**8,2**	
CD34 pre [/µl]	**82**	
kg BW	**84**	
Size [cm]	**184**	
female?	**FALSCH**	
BV acc Nadler [l]	5,594	
max processed [fold BV]	6	33562
max time [h]	6	



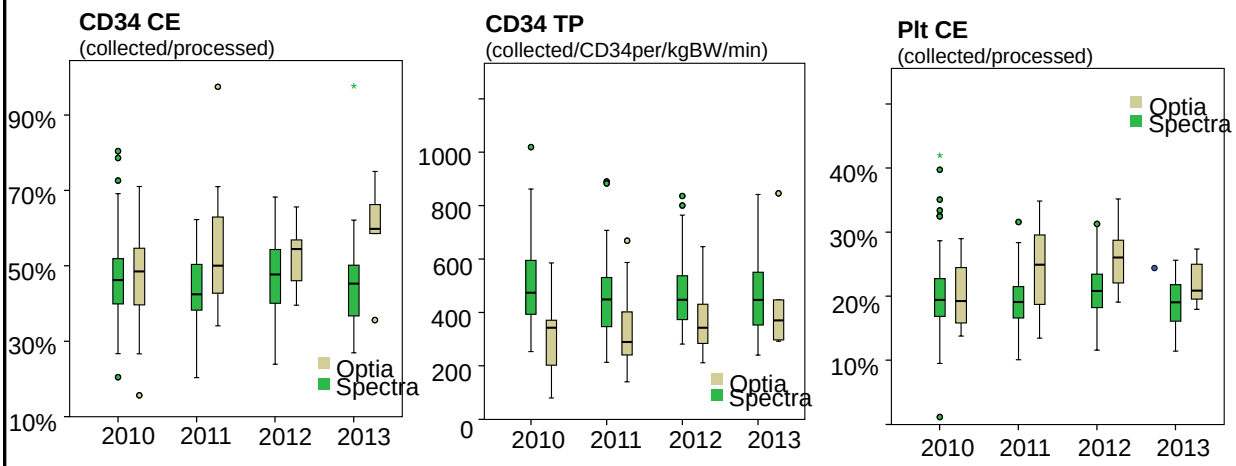
Performance Measurement for devices

- **Collection efficiency (CE)**
  - Defined as
    collected cells /
    (peripheral count x processed blood volume)

CE1
based on pre and post count
CE2
based on pre count only

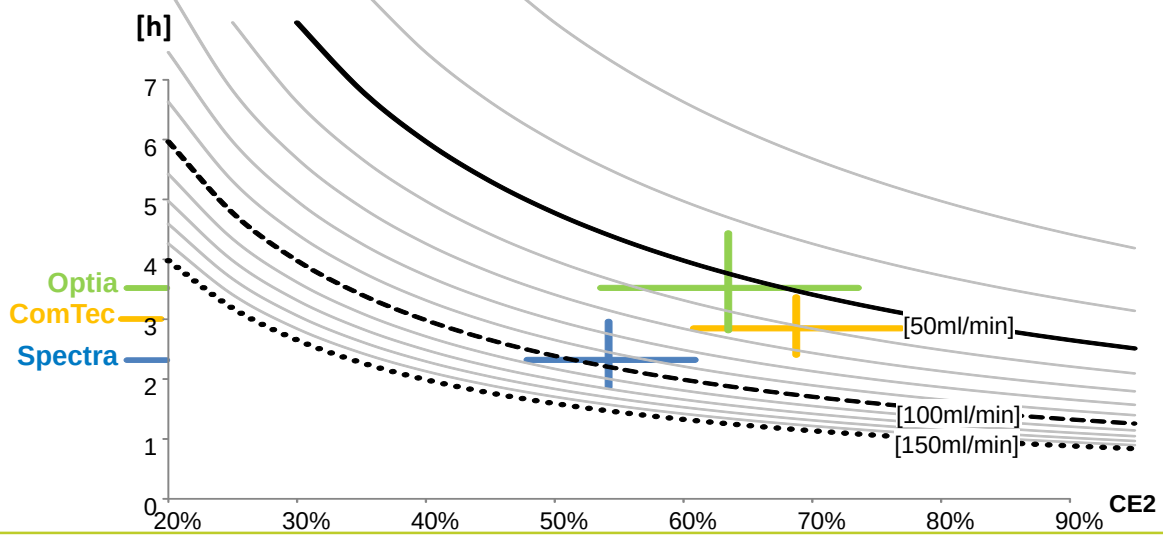
- **Throughput (TP)**
  - cells collected /kg BW/ hour/ mean peripheral count
  - at a TP= 0.02:
  - **0.2**CD34x10^6/kg BW will be collected per **h** and per **10** CD34/µl PB

DUS Data



DUS/ Cellex Cohort

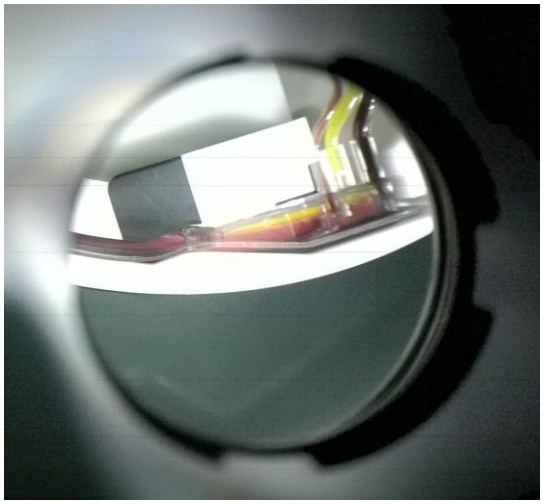
Apheresis-duration using mean values: 8.2 x 10^6 CD34/kg BW, 82 CD34/µl in PB, 82kg, 179cm



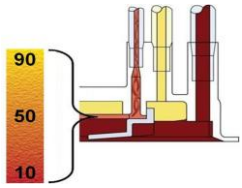
Apheresis Device

- **MNC Optia, ComTech**
  - High CE2 Conclusion
  - High PLT loss
  - Low CD34 TP
- **Spectra manual MNC**
  - High CD34 TP
  - Low PLT Loss

Termo BCT Optia Device



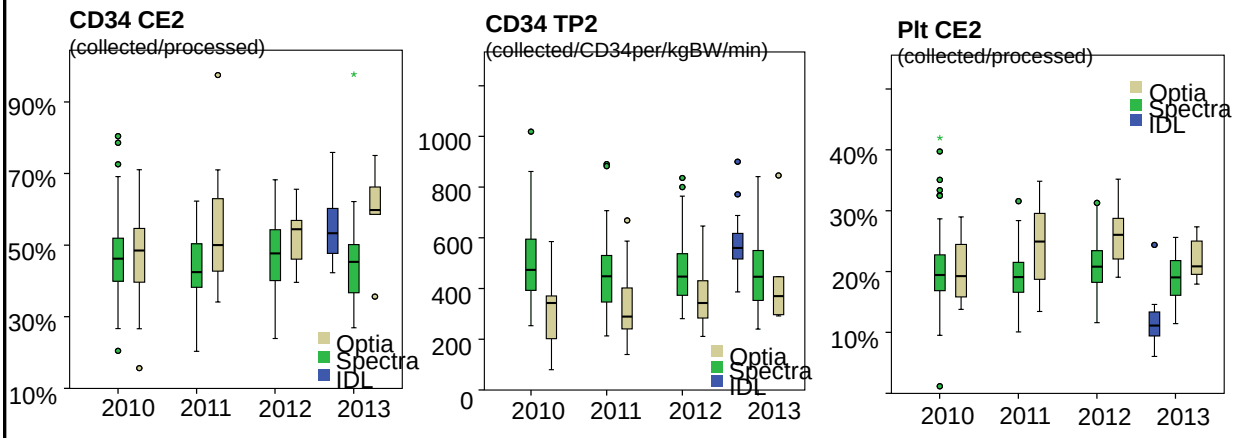
IDL/cMNC



Pilot-Study, IDL Disposable, WBC-D SW

- Apheresis
  - PF 4
  - Collection pump .8
  - Preference slightly darker than used on Cobe Spectra
  - ACDA 1:12 up to 1:30, heparinization
- End of run
  - Dilution of the product with plasma
  - PF 10
  - Preference as low as possible
  - Collection pump 50% of previous plasma pump rate
- Sampling
  - PB: Pre, mid, post
  - Product: mid, post

DUS experience: IDL-pilot



optiMaL IDNC

Prospective Randomized Trial Comparing Efficiency of Peripheral Blood Progenitor Cell Collection in Allogeneic Donors Using the Spectra Optia® IDL Set in Comparison With the Spectra Optia® MNC Collection Set

(EUDAMED CIV-13-10-011663; http://clinicaltrials.gov/ct2/show/NCT01901458)

- Inclusion
  - G-CSF mobilized allo donor at d5 of mobilization
  - 1st apheresis in mob cycle
- Exclusion
  - Plasma collection
  - Other study
  - 2nd apheresis

n	IDL			MNC		
		DUS	Clx		DUS	Clx
randomization	25	11	14	25	11	14
apheresis	25	11	14	24	11	13
30d safety	25	11	14	23	10	13

Results

target		CE1 [%]			TP1 [/kg BW/h/µl]			Further parameter		
MNC	+									
CD34	+									
Ly	+									
T	~									
B	~									
NK	+									
Gran	-									
hb	-									
Plt	-									

* < 0.05, ** < 0.01, *** < 0.001, etc. , # calculated as per µl

Results

target		CE1 [%]			TP1 [/kg BW/h/µl]			Further parameter		
		IDL	MNC	p						
MNC	+	**62.1**	54.8	***						
CD34	+	**74.3**	67.5	*						
Ly	+	**73.0**	55.8	**						
T	~	92.5	94.4	n.s.						
B	~	85.7	91.4	n.s.						
NK	+	70.2	77.3	n.s.						
Gran	-	2.99	**8.84**	****						
hb	-	.060	**.108**	****						
Plt	-	14.5	30.3	****						

* < 0.05, ** < 0.01, *** < 0.001, etc. , # calculated as per µl

Results

target		CE1 [%]			TP1 [/kg BW/h/µl]			Further parameter		
		IDL	MNC	p	IDL	MNC	p			
MNC	+	**62.1**	54.8	***	**.042**	.022	****			
CD34	+	**74.3**	67.5	*	**.042**	.026	****			
Ly	+	**73.0**	55.8	**	**.042**	.022	****			
T	~	92.5	94.4	n.s.	**.054**	.038	***			
B	~	85.7	91.4	n.s.	**.022**	.015	**			
NK	+	70.2	77.3	n.s.	.034	.030	n.s.			
Gran	-	2.99	**8.84**	****	.0016	.0034	****			
hb	-	.060	**.108**	****	6E-06#	**10E-06**	****			
Plt	-	14.5	30.3	****	8E-03	**12E-03**	****			

* < 0.05, ** < 0.01, *** < 0.001, etc. , # calculated as per µl

Results

target		CE1 [%]			TP1 [/kg BW/h/µl]			Further parameter		
		IDL	MNC	p	IDL	MNC	p	IDL	MNC	p
MNC	+	**62.1**	54.8	***	**.042**	.022	****	**78.2**	52.9	[% of WBC] ****
CD34	+	**74.3**	67.5	*	**.042**	.026	****			
Ly	+	**73.0**	55.8	**	**.042**	.022	****			
T	~	92.5	94.4	n.s.	**.054**	.038	***			
B	~	85.7	91.4	n.s.	**.022**	.015	**			
NK	+	70.2	77.3	n.s.	.034	.030	n.s.			
Gran	-	2.99	**8.84**	****	.0016	.0034	****			
hb	-	.060	**.108**	****	6E-06#	**10E-06**	****			
Plt	-	14.5	30.3	****	8E-03	**12E-03**	****	26.2	**41.8**	[% loss] ***

* < 0.05, ** < 0.01, *** < 0.001, etc. , # calculated as per µl

Conclusion of the Optimal study

- Our center's experience shows that cMNC is more efficient than MNC on Spectra OPTIA © in the following areas:
  - less PLT loss
  - higher CD34 CE
  - higher CD34 TP

Factors Influencing Performance of OPTIA cMNC

n=153	CE2			TP2		
	preferable	p	r^2	preferable	p	r^2
pre WBC						
pre CD34						
Inlet BV						
Don BV						
male/female						

Factors Influencing Performance of OPTIA cMNC

n=153	CE2			TP2		
	preferable	p	r^2	preferable	p	r^2
pre WBC		<0.004	0.049			
pre CD34		<0.001	0.185			
Inlet BV		<0.001	0.315			
Don BV						
male/female		<0.03	0.03			
		<0.001	0.319			

Factors Influencing Performance of OPTIA cMNC

n=153	CE2			TP2		
	preferable	p	r^2	preferable	p	r^2
pre WBC	low	<0.004	0.049			
pre CD34	low	<0.001	0.185			
Inlet BV	low	<0.001	0.315			
Don BV	high					
male/female	male	<0.03	0.03			
		<0.001	0.319			

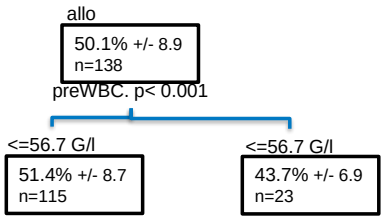
Factors Influencing Performance of OPTIA cMNC

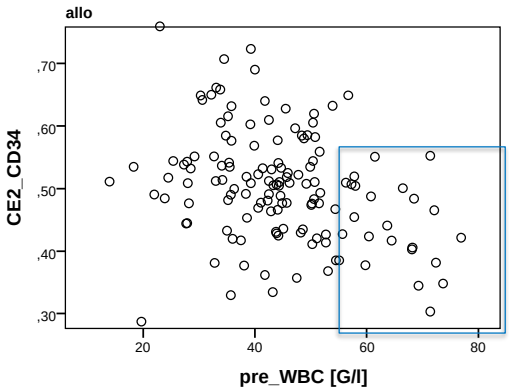
n=153	CE2			TP2		
	preferable	p	r^2	preferable	p	r^2
pre WBC	low	<0.004	0.049		<0.045	0.017
pre CD34	low	<0.001	0.185		<0.001	0.077
Inlet BV	low	<0.001	0.315		<0.001	0.391
Don BV	high				<0.001	0.668
male/female	male	<0.03	0.03		<0.001	0.145
		<0.001	0.319		<0.001	0.480

Factors Influencing Performance of OPTIA cMNC

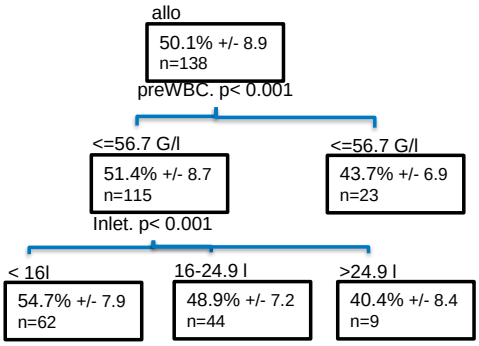
n=153	CE2			TP2		
	preferable	p	r^2	preferable	p	r^2
pre WBC	low	<0.004	0.049	low	<0.045	0.017
pre CD34	low	<0.001	0.185	low	<0.001	0.077
Inlet BV	low	<0.001	0.315	high	<0.001	0.391
Don BV	high			low	<0.001	0.668
male/female	male	<0.03	0.03	female	<0.001	0.145
		<0.001	0.319		<0.001	0.480

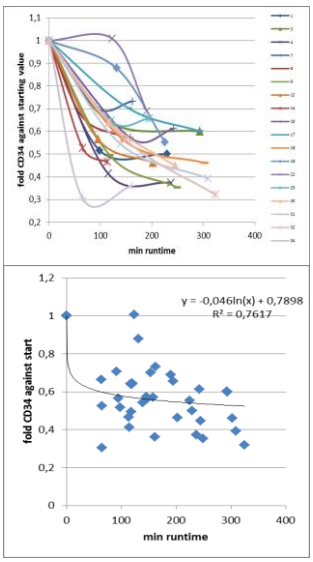
CHAID Analysis (CE2)



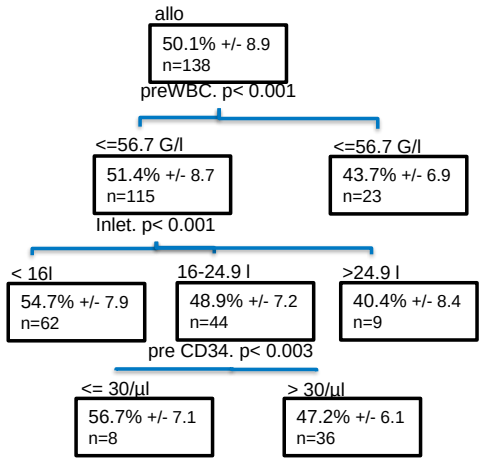


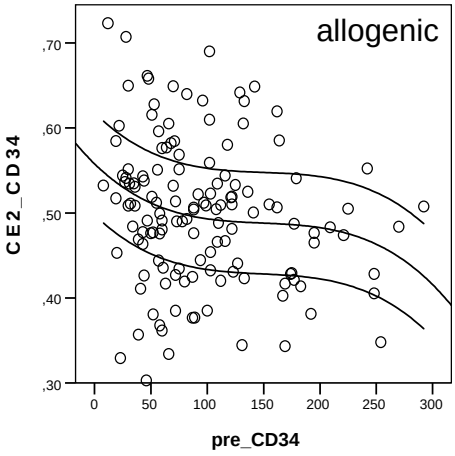
CHAID Analysis (CE2)



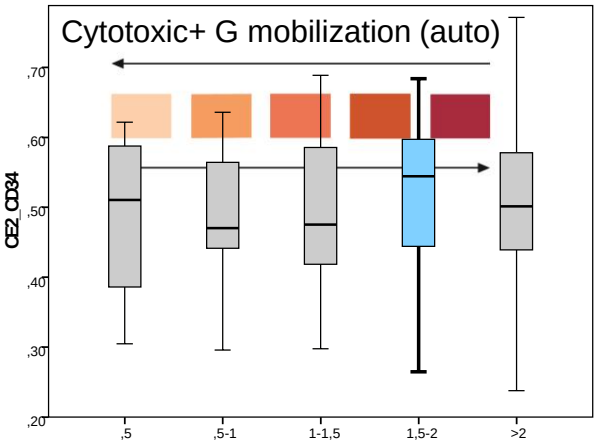


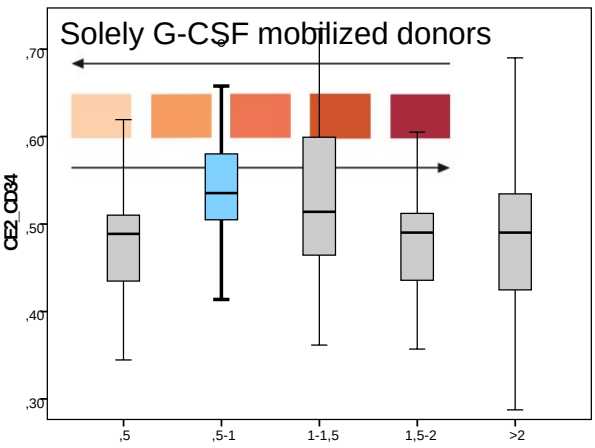
CHAID Analysis (CE2)





Preference to choose

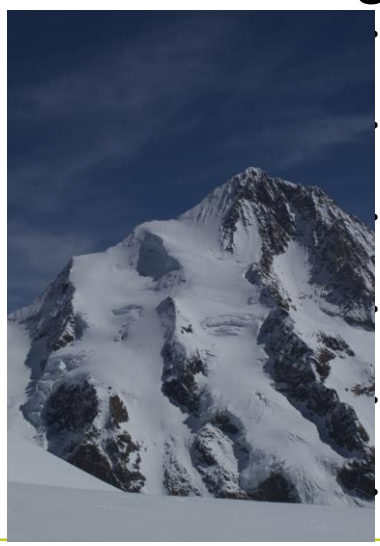




Results of CHAID Analysis on Optia cMNC CE2 Data

- High WBC Count
  - Increase sample flow (0.8 -> 1ml/min)
- Most cells can be collected within the first hour of Apheresis
  - Try to get stable conditions as soon as possible
- In high CD34 counts CE drops slightly
  - You do not have to care in this cases
- Collection Preference
  - Slightly darker than used in the old Spectra days.

Acknowledgments



- **ITZ, HHU Düsseldorf**
  Jutta M. Rox, Johannes C. Fischer + Team
- **Cellex GmbH, Köln**
  Michael Punzel, Helmuth Schmidt + Team
- **KKS, HHU Düsseldorf**
  Ch.Ohmann, D. Schilken
- *** Chugai**
  Grant
- *** STAR eV**
  Förderverein Stammzellspende Rheinland
- *** Terumo BCT**
  Grant