Phase 1 Clinical Study of MGTA-145 in Combination with Plerixafor Shows Rapid Single-Day Mobilization and Collection of CD34+ HSCs without G-CSF

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Washington University School of Medicine

February 22, 2020

Magenta Therapeutics

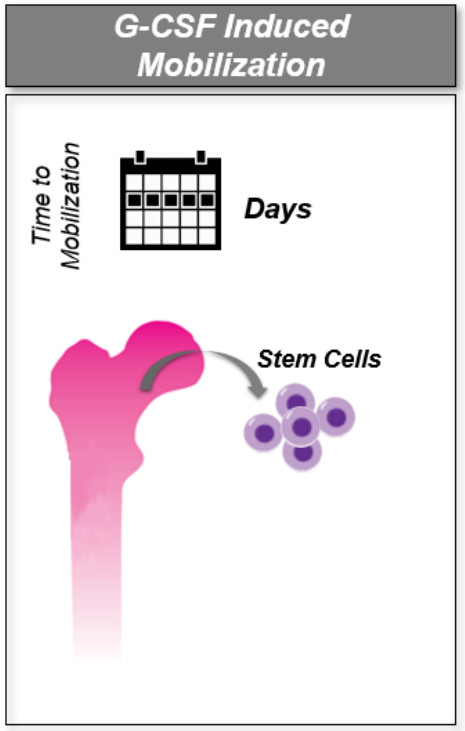
Disclosures

- **Consulting/Advisory Committees:** Cellworks, Tioma, Rivervest, Bioline, Asterias, Amphivena and Bluebird, Celgene, Incyte, NeoImmuneTech, Macrogenics
- **Employment/Salary:** Washington University
- **Ownership Investment** : Magenta, WUGEN

Background

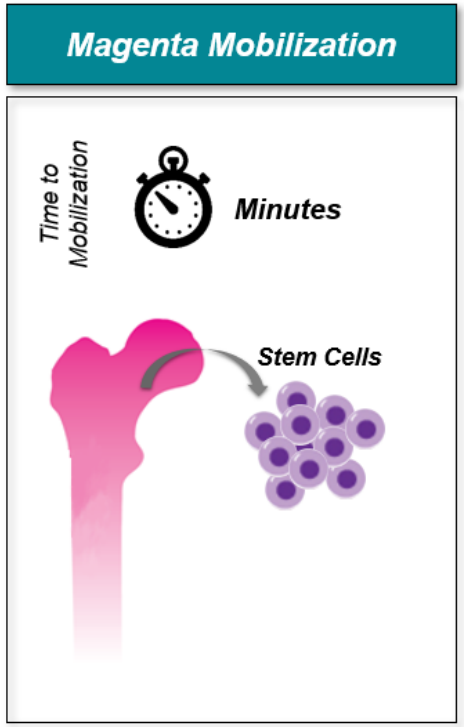
- MGTA-145 is a biologic agent that activates the CXCR2 pathway in neutrophils. In combination with plerixafor, a CXCR4 inhibitor, MGTA-145 can mobilize adequate numbers of HSCs for a successful transplant (≥2x10^6 $CD34^+$cells/kg) [Stiff et al, *BBMT* 2011].

- MGTA-145 plus plerixafor has been shown to rapidly mobilize HSCs in mice and non-human primates within minutes to hours, respectively [Hoggatt et al, *Cell* 2018; Goncalves et al, *Blood* 2018; Karpova et al, *JCI* 2019].



Limitations to Current Mobilization Standard of Care:
- Requires 4-6 days
- Adverse events, some for the duration of mobilization
- Variable yields
- Contraindicated/precautions in certain diseases

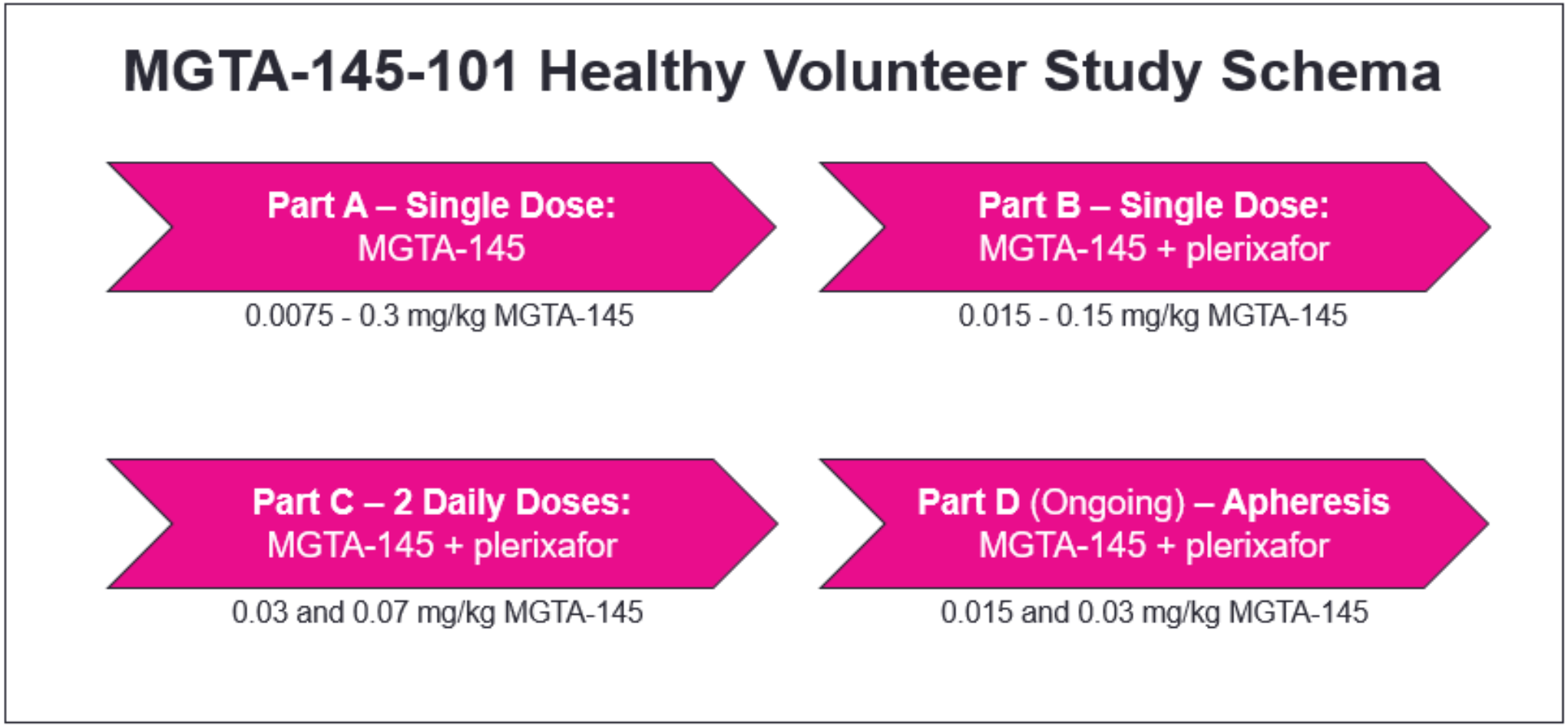
Benefits of Novel Mobilization:
- Shorten mobilization phase
- Fewer/shorter duration of adverse events
- On demand mobilization enables more flexible scheduling



Objectives

- To assess the safety and tolerability of MGTA-145 ± plerixafor
- To assess $CD34^+$ and $CD34^+CD90^+$ HSC mobilization after MGTA-145 ± plerixafor
- To assess the number of $CD34^+$ HSCs mobilized and collected during apheresis with MGTA-145 + plerixafor

Study Design



Subject Demographics

		Part A		Part B		Part C		Part D
		MGTA-145 (0.0075 – 0.3 mg/kg) n=24	**Placebo** n=12	**MGTA-145 + plerixafor** (0.015 – 0.15 mg/kg) n=38	**Plerixafor** n=14	**MGTA-145 + plerixafor** (0.03 – 0.07 mg/kg) n=8	**Plerixafor** n=2	**MGTA-145 + plerixafor** (0.015 – 0.03 mg/kg) n=8*
Age, years (range)		43 (27 – 59)	40 (22 – 54)	39 (22 – 59)	37 (18 – 59)	35 (24 – 57)	35 (24 – 41)	39 (24-54)
Male (%)		20 (83)	8 (67)	30 (79)	11 (79)	8 (100)	1 (50)	7 (78)
Weight, kg (range)		85 (57 – 111)	83 (59 – 97)	82 (54 – 107)	78 (58 – 106)	77 (63 – 97)	77 (63 – 88)	81 (72-94)
Race, n	White	14	5	12	6	4	1	7
	Black/AA	7	6	24	7	4	1	2
	Other	3	1	2	1	0	0	0

* A 9th subject enrolled in Part D but did not undergo leukapheresis

Treatment Emergent Adverse Events

	Part A		Part B		Part C		Part D
	MGTA-145 (0.0075 - 0.3 mg/kg)	**Placebo**	**MGTA-145 + plerixafor** (0.015 - 0.15 mg/kg)	**Plerixafor**	**MGTA-145 + plerixafor** (0.03 - 0.07 mg/kg)	**Plerixafor**	**MGTA-145 + plerixafor** (0.015 - 0.03 mg/kg)
	n=24	n=12	n=38	n=14	n=8	n=2	n=8*
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with any drug related TEAE	**19 (79.2)**	**-**	**31 (81.6)**	**8 (57.1)**	**6 (75.0)**	**-**	**8 (88.9)**
Diarrhea	-	-	6 (15.8)	5 (35.7)	1 (12.5)	-	1 (11.1)
Nausea	-	-	7 (18.4)	2 (14.3)	1 (12.5)	-	4 (44.4)
Abdominal discomfort/pain	-	-	5 (13.2)	4 (28.6)	-	-	3 (33.3)
Vomiting	-	-	3 (7.9)	1 (7.1)	-	-	1 (11.1)
Back pain / Musculoskeletal pain[2]	19 (79.2)	-	24 (63.2)	2 (14.3)	4 (50.0)	-	3 (33.3)
Dizziness / Lightheadedness	-	-	5 (15.6)	1 (7.1)	-	-	4 (44.4)
Headache	-	-	4 (10.5)	1 (7.1)	2 (25.0)	-	2 (22.2)
Dysgeusia	-	-	-	2 (14.3)	-	-	-
Paraesthesia	-	-	2 (5.3)	-	1 (12.5)	-	1 (11.1)

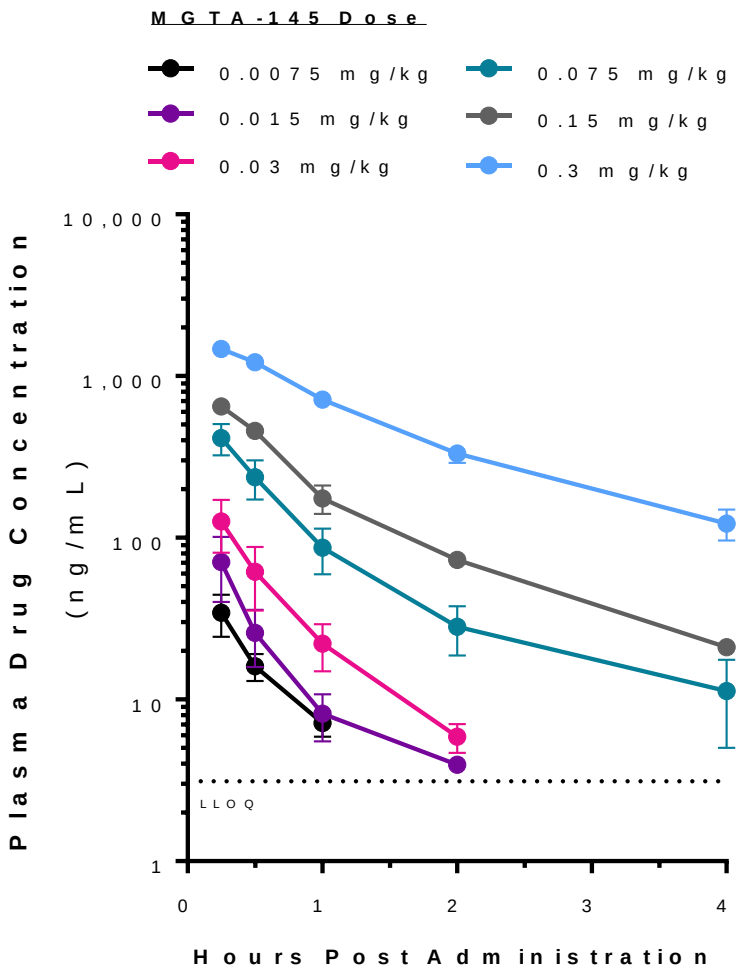
There was no dose response in AEs, so data are aggregated.

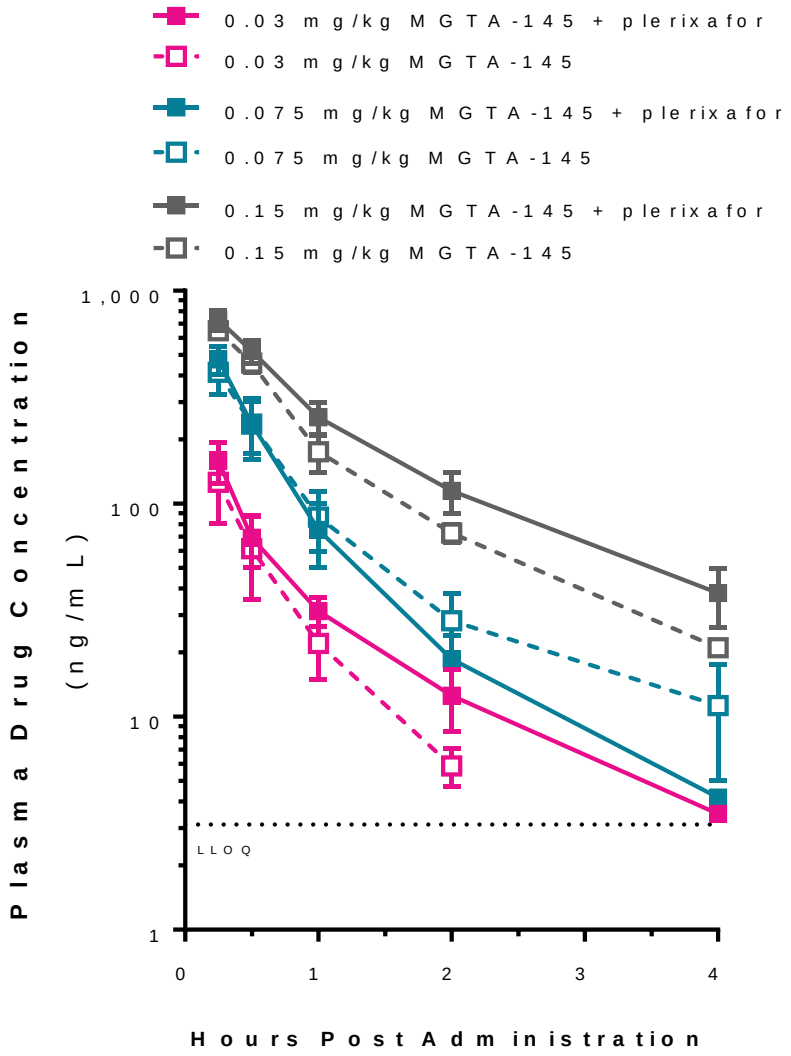
[1] All AEs are grade 1 except for grade 2 abdominal pain (1), nausea (1), and back pain (1) in the plerixafor + MGTA-145 0.075 mg/kg 2h stagger cohort (Part B) and grade 2 headache (1) in the plerixafor + MGTA-145 0.015 mg/kg cohort (Part D).

[2] Back pain was associated with MGTA-145 infusion, lasted <20 minutes in most cases and did not require medical therapy.

* A 9th subject enrolled in Part D but did not undergo leukapheresis.

Pharmacokinetics of MGTA-145 Alone and in Combination with Plerixafor





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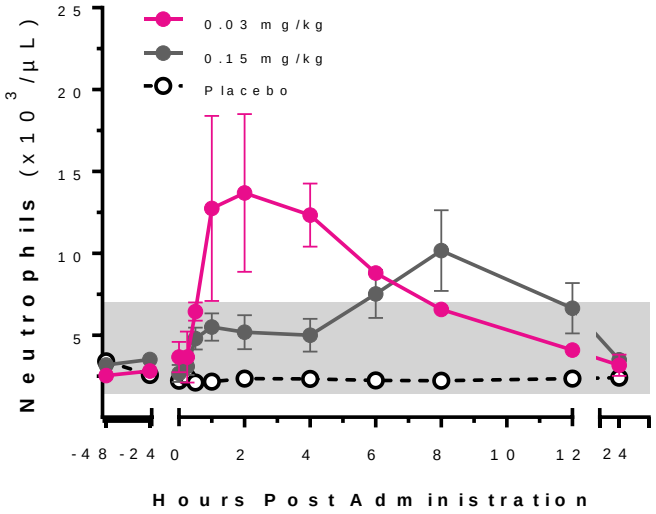
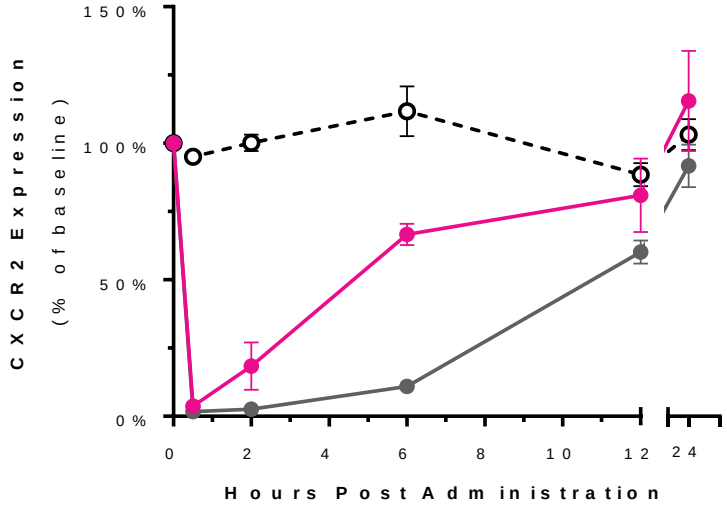
MGTA-145 has Rapid On-Target Neutrophil PD with Minimal Activation

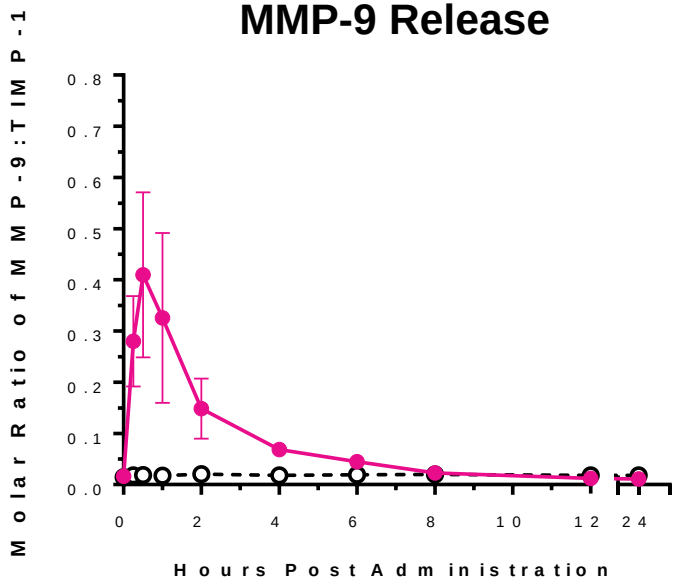
Neutrophil Mobilization



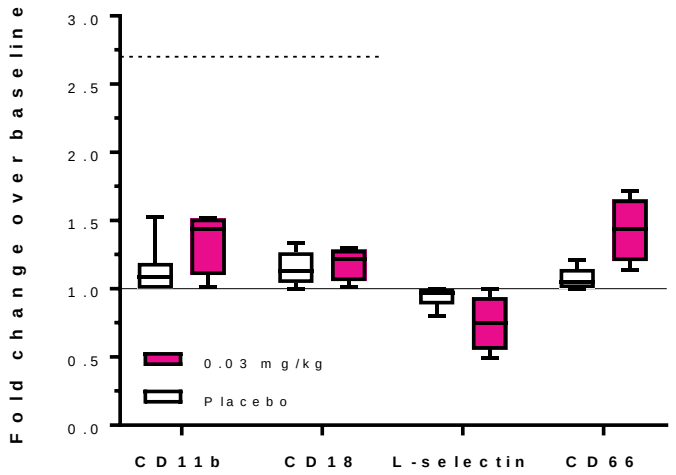
CXCR2 Target Down-Modulation



MMP-9 Release



Minimal Neutrophil Activation



Dotted line represents the anticipated effect of 5 days of G-CSF [Falanga *et al*., *Blood*. 1999]

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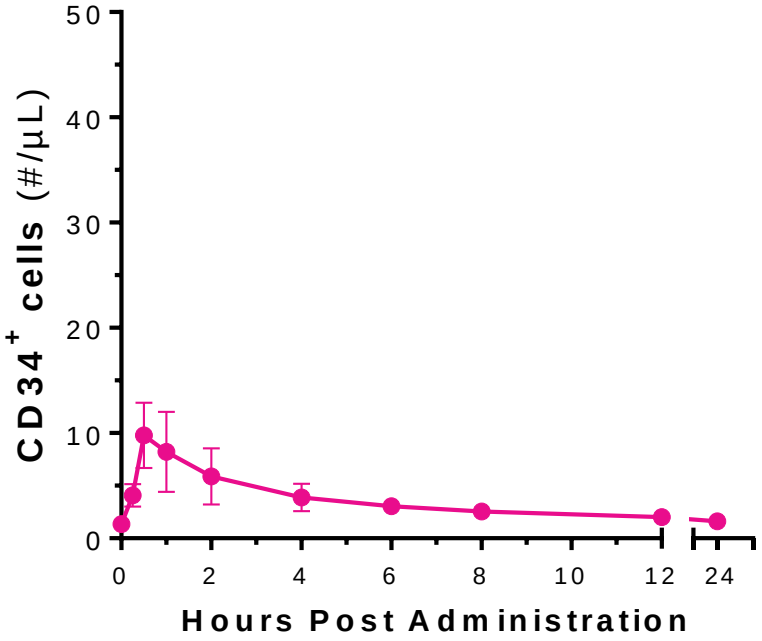
MGTA-145 Demonstrates Single Agent Activity and Leads to Robust Mobilization of CD34+ Cells in Healthy Subjects in Combination with Plerixafor

MGTA-145 Monotherapy

MGTA-145 + plerixafor

A



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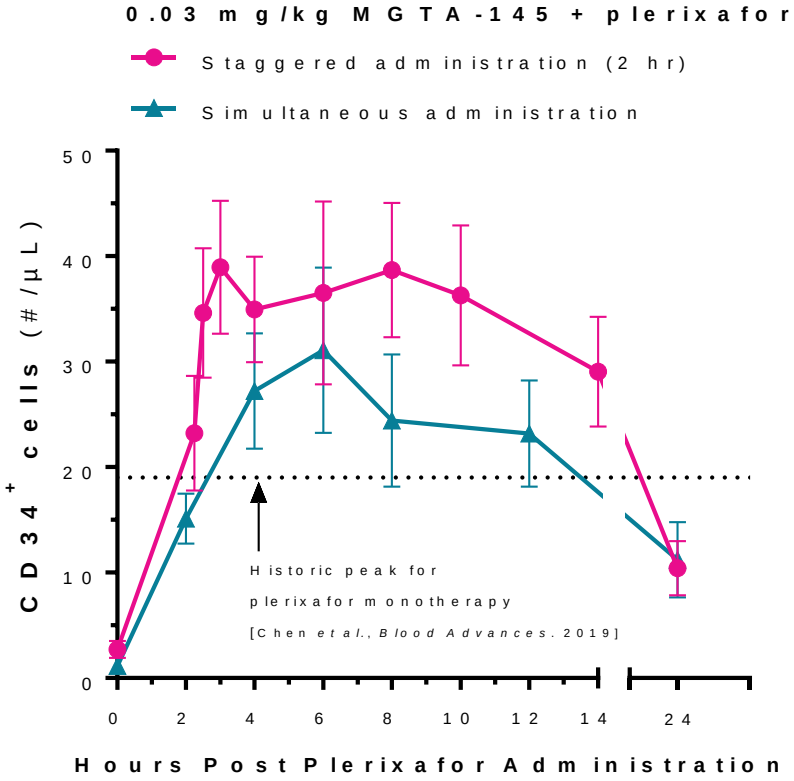

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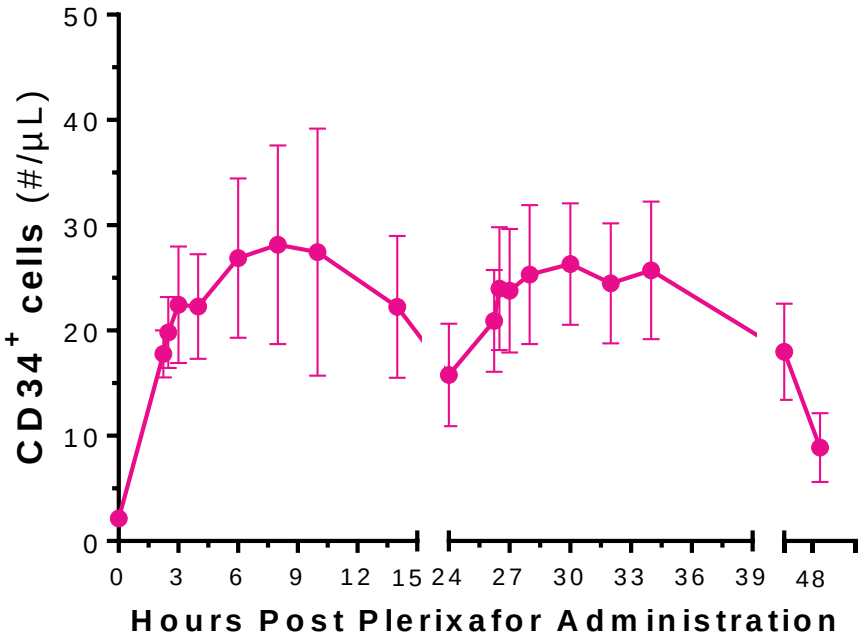


MGTA-145 Reliably Mobilizes >20 CD34^{+} Cells per µL

Part B: Mobilization at 0.015 versus 0.03 mg/kg, 2h stagger

Mobilization Regimen	**MGTA-145 dose** (mg/kg)	**Subjects** (n)	**Peak CD34^{+}** (#/µL) Median (range)	**% ≥ 20** / µL	**% ≥ 40** / µL
MGTA-145 + Plerixafor	0.015	6	**35** (17-78)	**83%** (5/6)	**33%** (2/6)
	0.03	6	**40** (18-63)	**83%** (5/6)	**50%** (3/6)
Plerixafor	0	14	**26** (13-78)	**64%** (9/14)	**21%** (3/14)

MGTA-145 Enabled Reliable Collection of >2x10^6 CD34$^+$ Cells in One Day

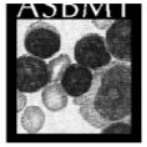
Part D: Apheresis Collection at 0.015 versus 0.03 mg/kg dose, 2h stagger

MGTA-145 dose (mg/kg)	**Subjects** (n)	**Total CD34$^+$ Yield** (x10^6) Median (range)	**CD34$^+$ / kg** (x10^6)			**CD90$^+$ / kg** (x10^6)[a]			**CD90$^+$** (% of CD34$^+$)
			Mean	Median	Range	Mean	Median	Range	
0.015	4	310 (118-525)	4.0	3.7	1.5 - 7.0	1.4	1.2	0.5 – 2.8	37%
0.03	4	321 (239-500)	4.1	4.3	2.7 – 5.3	1.3	1.5	0.5 – 1.8	31%

Collection data reflect internal analysis.

[a] CD90$^+$ cells defined as CD34$^+$ CD90$^+$ CD45RA$^-$ cells.

CD34+ CD90+ Cells Contain Hematopoietic Stem Cells Responsible for Robust Engraftment in Humans and Non-human Primates



Transplantation of Highly Purified CD34+Thy-1+ Hematopoi
Breast Can

Robert S.
Wendy W
Irving L.
William

ELSEVIER

EXPERIMENTAL HEMATOLOGY

Experimental Hematology 28 (2000) 858–870

Transplantation with selected autologous peripheral blood CD34+Thy1+ hematopoietic stem cells (HSCs) in multiple myeloma: Impact of HSC dose on engraftment, safety, and immune reconstitution

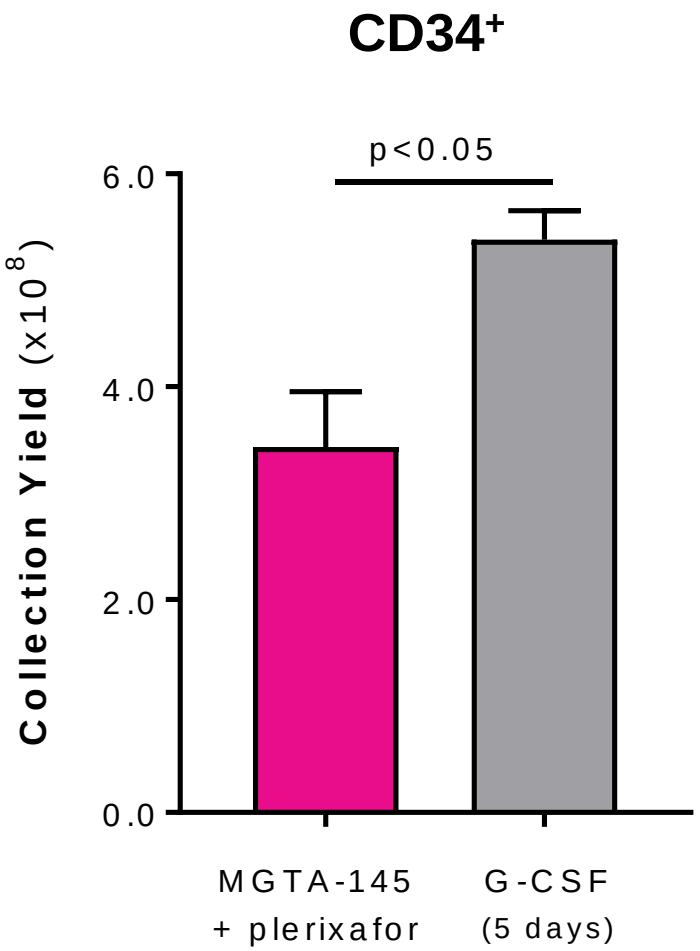
Maur
Catherine
Philippe Maz
Gilbert Fine[c], Kerry A

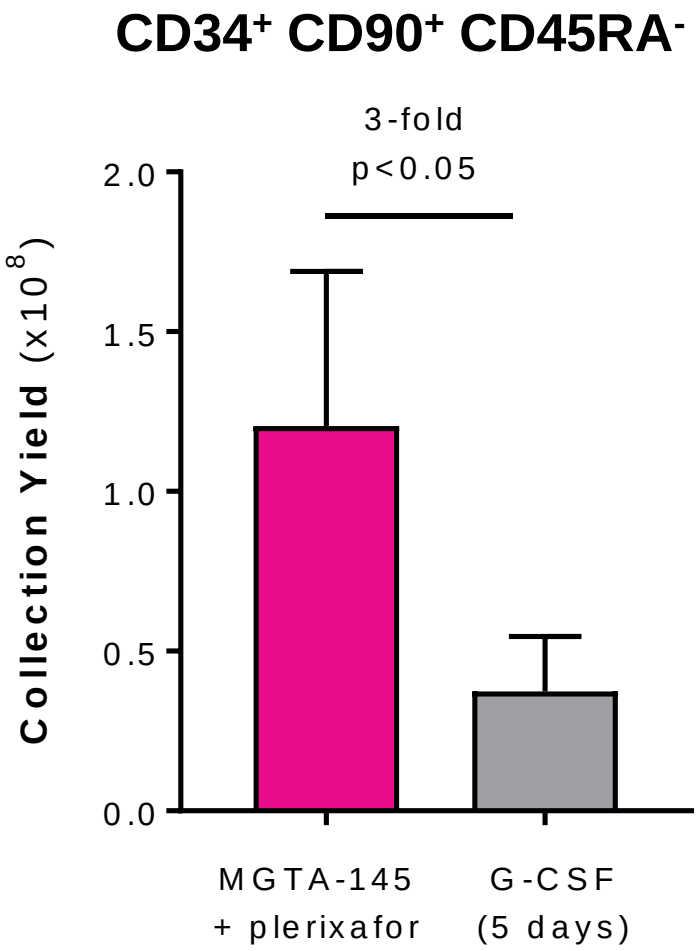
Sci Transl Med. 2017 November 01; 9(414): . doi:10.1126/scitranslmed.aan1145.

A distinct hematopoietic stem cell population for rapid multilineage engraftment in nonhuman primates

Stefan Radtke[#1,2], Jennifer E. Adair[#1,3], Morgan A. Giese[1], Yan-Yi Chan[1], Zachary K. Norgaard[1], Mark Enstrom[1], Kevin G. Haworth[1], Lauren E. Schefter[1], and Hans-Peter Kiem[1,3,4,*]

MGTA-145 + Plerixafor Mobilizes Higher Numbers of Phenotype HSCs Capable of Robust Multilineage Engraftment than Standard-of-Care

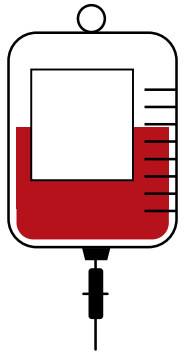




Data expressed as mean± 95% CI
MGTA-145 + plerixafor: n=7 donors (mobilized with 0.015 or 0.03 mg/kg MGTA-145)
G-CSF: n=3 donors

Significantly Higher Multilineage Engraftment of MGTA-145 + Plerixafor-Mobilized CD34+ Cells Compared to G-CSF-Mobilized CD34+ Cells in NSG Mice

Collect mobilized CD34+ cells



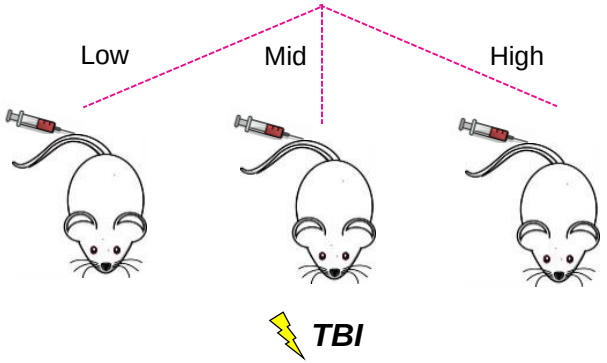
MGTA-145 + plerixafor Apheresis product (Part D)

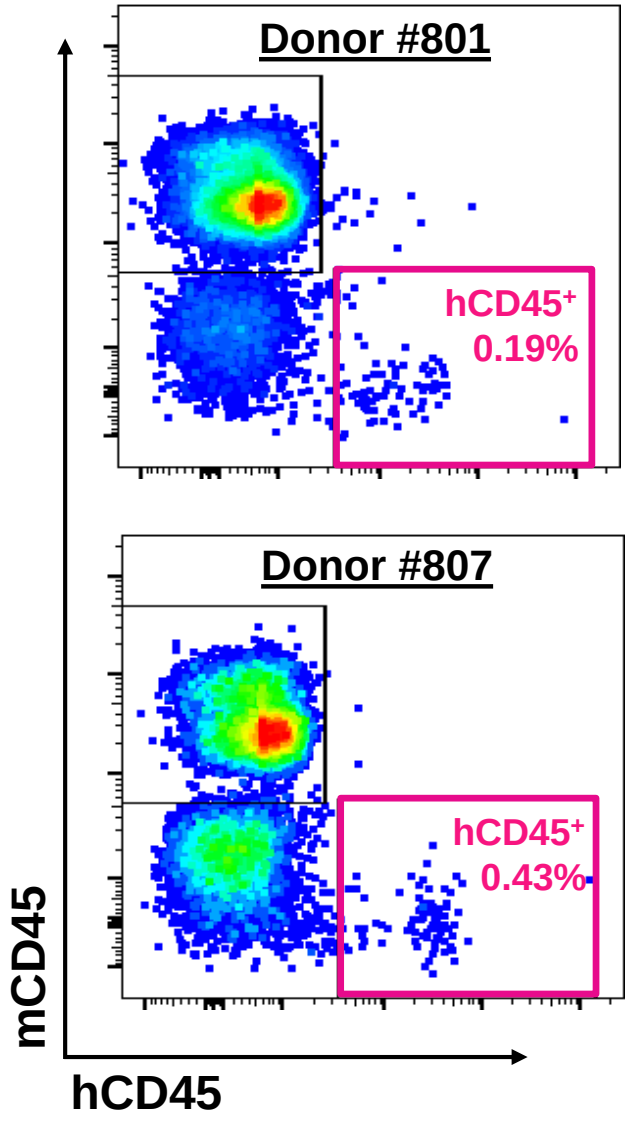
vs.

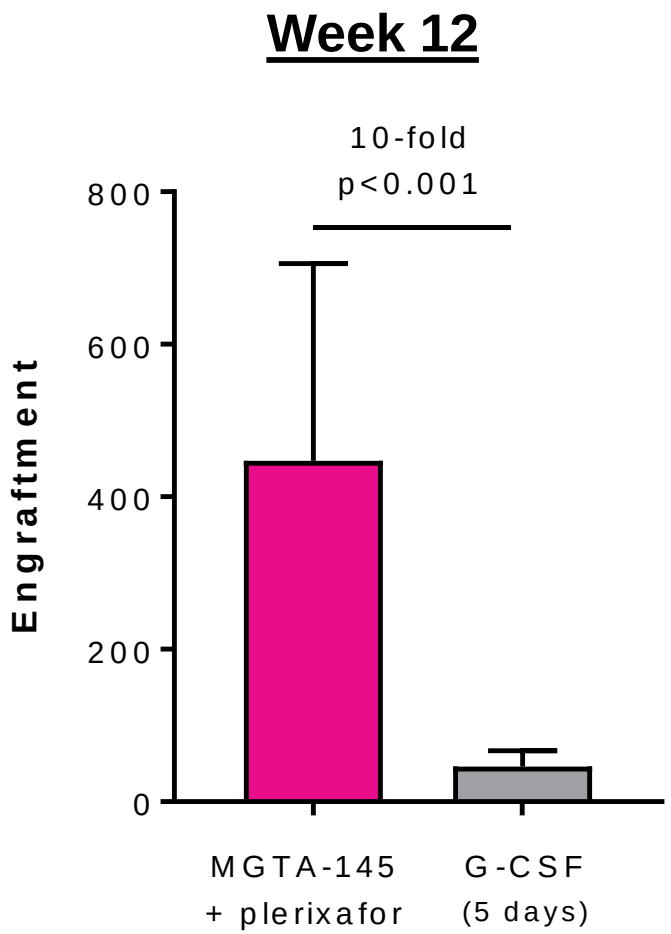
G-CSF-mobilized peripheral blood

Limiting Dilution Transplant into NSG mice

CD34+ cell doses







SRC ± 95% CI
MGTA-145 + plerixafor: n=2 donors (at 0.03 mg/kg dose level)
G-CSF: n=3 donors
n=7-8 mice per cell dose

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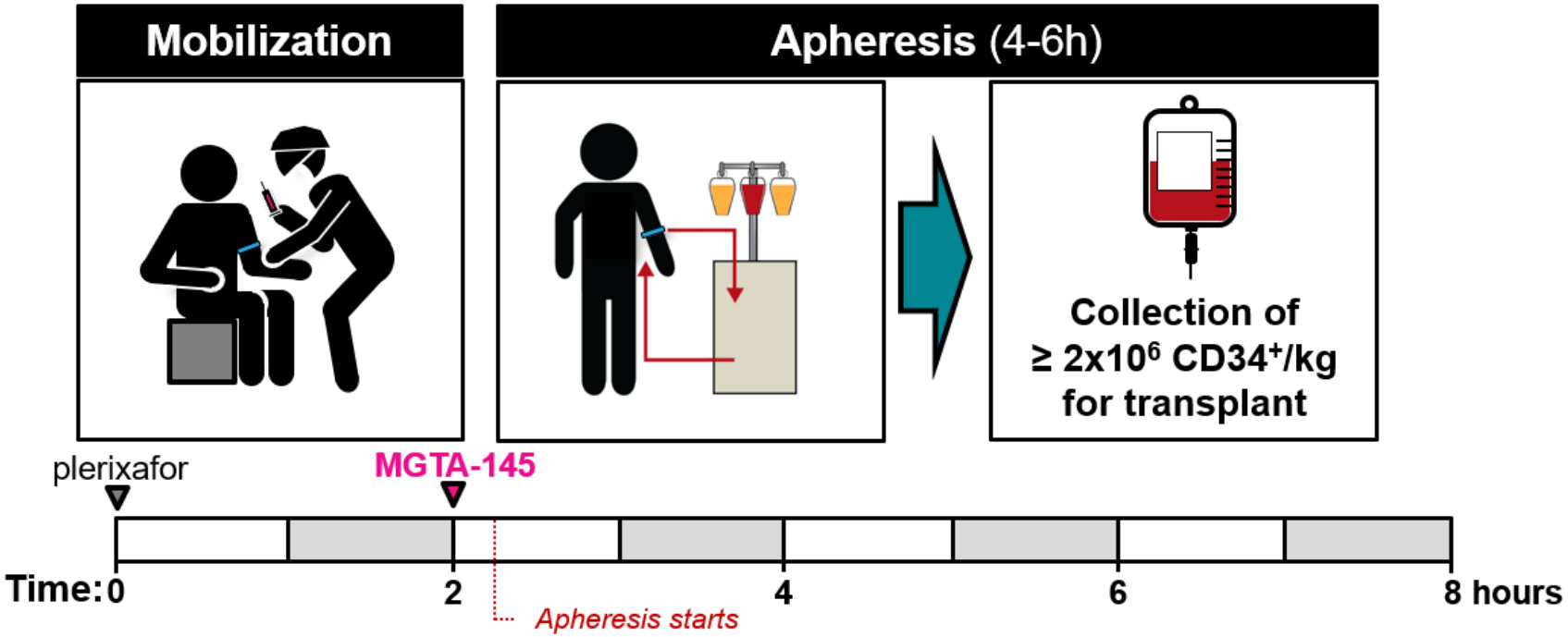
Summary

- MGTA-145 is well-tolerated in 79 subjects as monotherapy and in combination with plerixafor.
- MGTA-145 engages CXCR2 on neutrophils to mobilize $CD34^+$ cells into peripheral blood with limited neutrophil activation.
- MGTA-145 in combination with plerixafor reliably mobilizes sufficient HSCs for a transplant.
- After dosing and apheresis, preliminary data suggest that MGTA-145 + plerixafor mobilizes HSCs enriched in functional $CD34^+$ $CD90^+$ cells.



Conclusions

- MGTA-145 administration is safe, as monotherapy or in combination with plerixafor, and led to an additive increase in CD34$^+$ cell mobilization.
- Additional studies to fully characterize MGTA-145 + plerixafor apheresis products, including preclinical engraftment and graft versus host disease (GvHD) studies in mice, are ongoing.
- The number of functional stem cells mobilized by MGTA-145 + plerixafor provides a strong rationale for conducting mobilization studies of allogeneic and autologous transplant in autoimmune diseases, hematopoietic gene therapy and hematologic malignancies.

	G-CSF	MGTA-145 + plerixafor
Mechanism of action	Bone remodeling	Chemokine cell migration
Time to mobilize and collect	5+ days	<1 day
Tolerability	Majority with bone pain, headache, myalgia, and/or fatigue (up to 1+ week)[a]	Majority with transient, grade 1 back pain (most <20 minutes)
Efficacy (≥2x10^6 CD34$^+$/kg)	78%[b]	100% (4/4 at 0.03 mg/kg dose) 75% (3/4 at 0.015 mg/kg dose)
Functional CD34$^+$ (% CD90$^+$)	10%	35%
Engraftment of CD34$^+$	-	10x increased engraftment

[a] Pulsipher *et al.*, *Blood*. 2009; [b] Holig, *Transfus Med Hemother.* 2013.

Thank you

magenta THERAPEUTICS

- Pat Falahee
- Kevin Goncalves
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- Glen Raffel
- Veit Schmelmer
- Haley Howell
- Jason Neale
- Tony Boitano
- John Davis

BE THE MATCH®

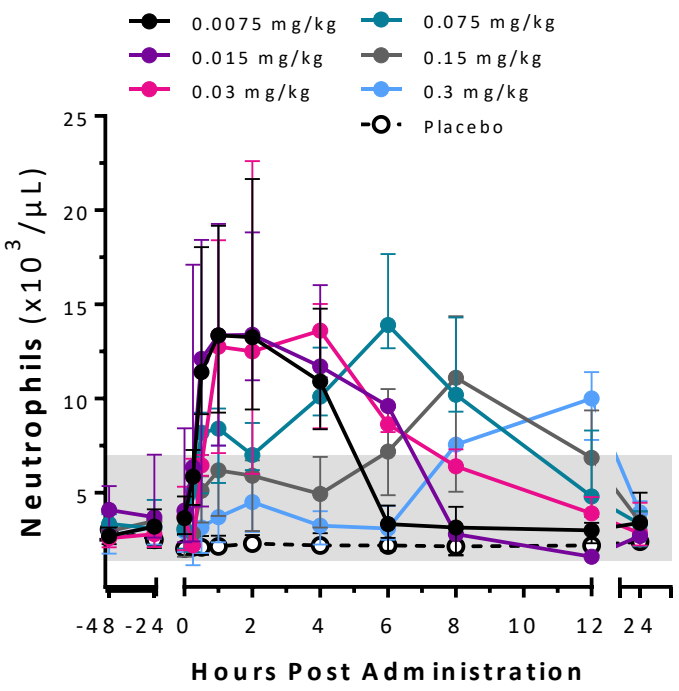
- Steve Devine

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL

- David Scadden
- Jon Hoggatt

Backup1: PD data for all dose levels

A



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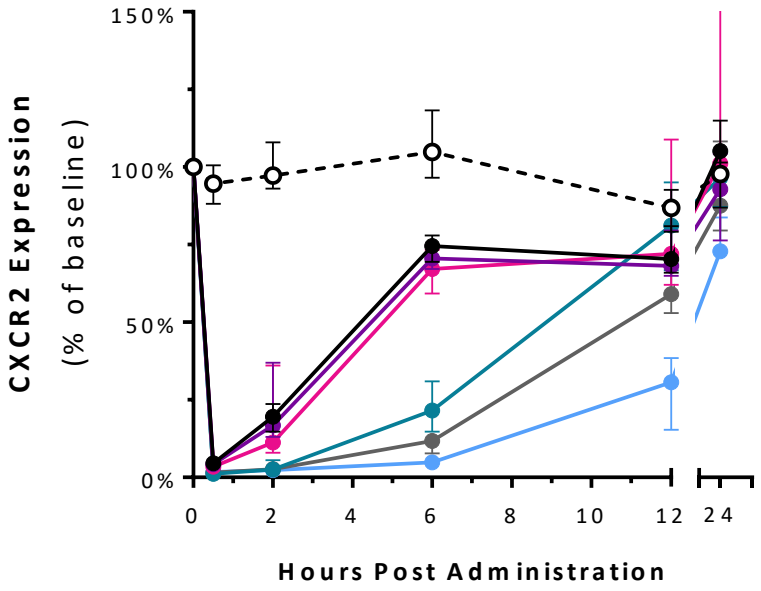

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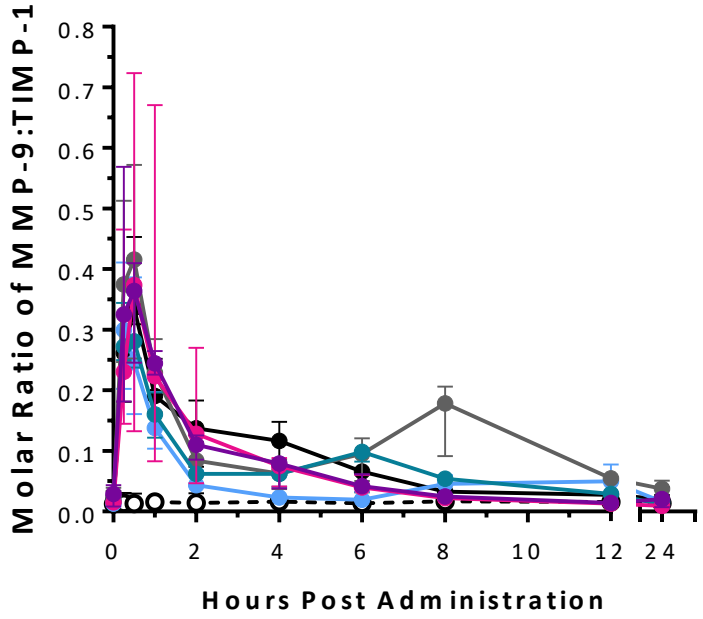

Backup2: Monotherapy data for all dose levels

MGTA-145 Monotherapy