Single cell analysis reveals immune dysfunction in Large B cell Lymphoma (LBCL) pts with hypomagnesemia receiving Axi-cel: results from ZUMA-1 trial and Mayo Clinic cohort

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Disclosures

None

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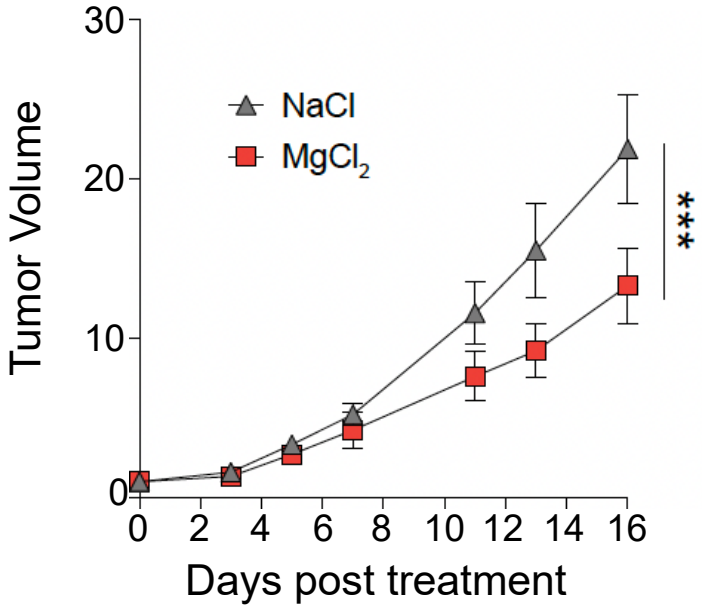
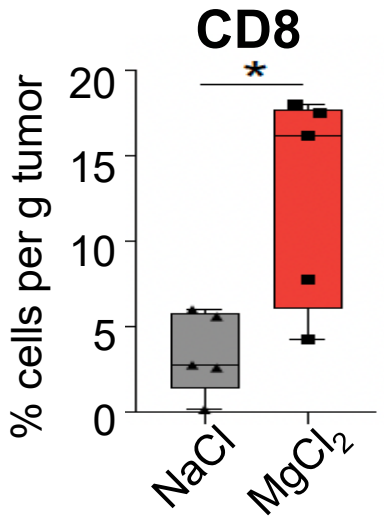
Magnesium levels affect T cell immune response





Nasulewicz, et al Biochim, Biophys. Acta 2004
Lotscher et al, Cell 2022

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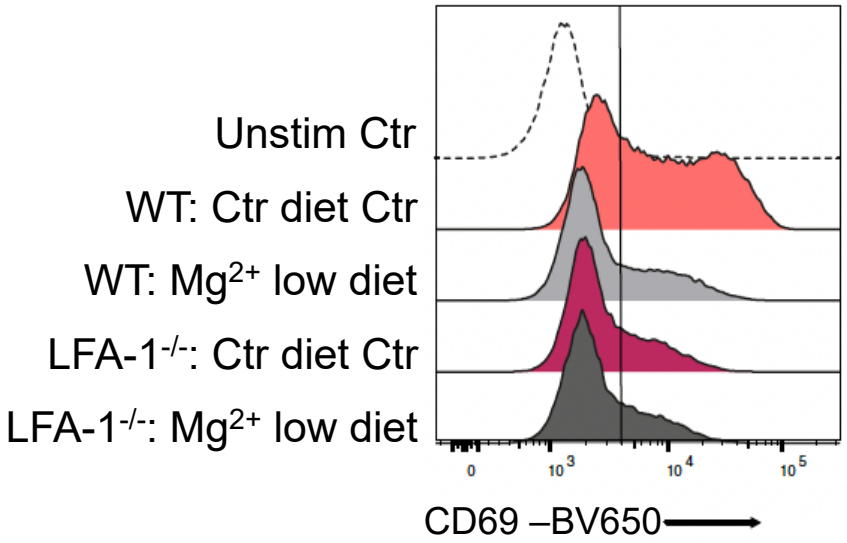

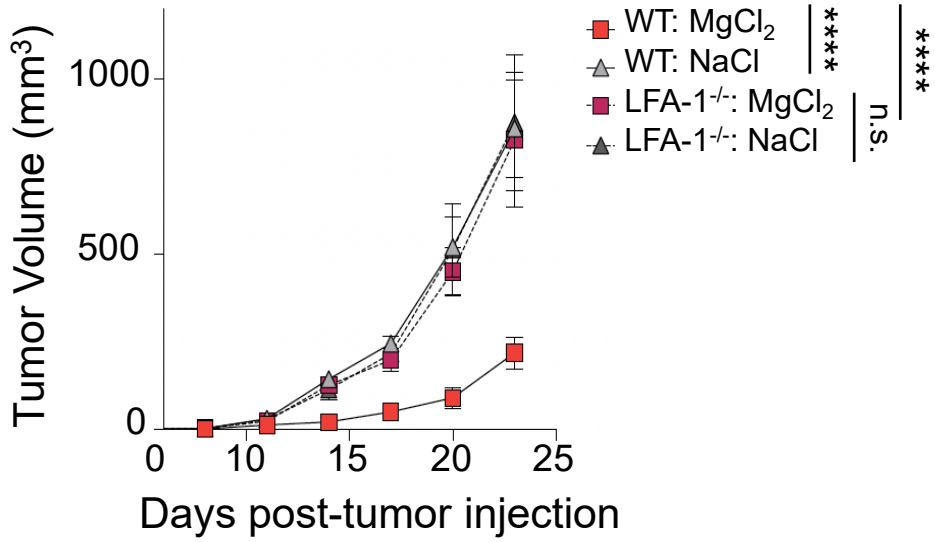

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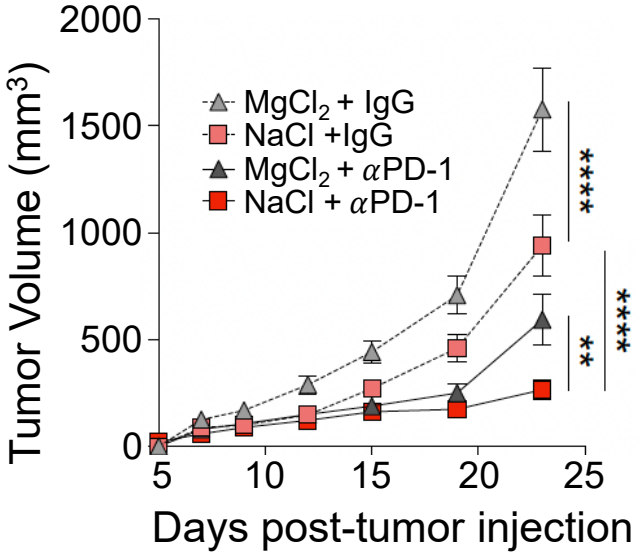
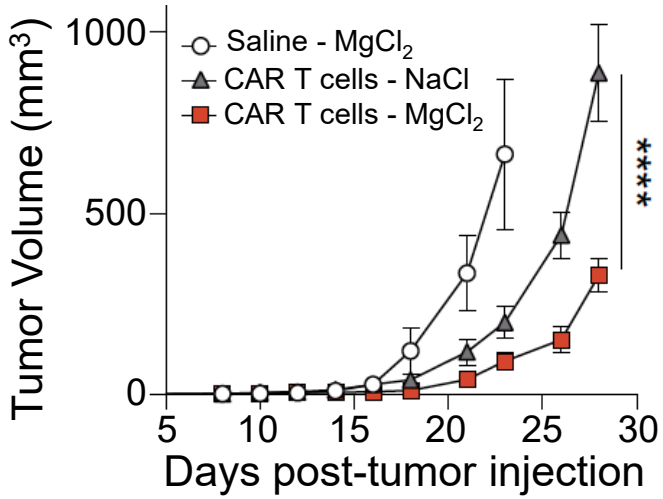
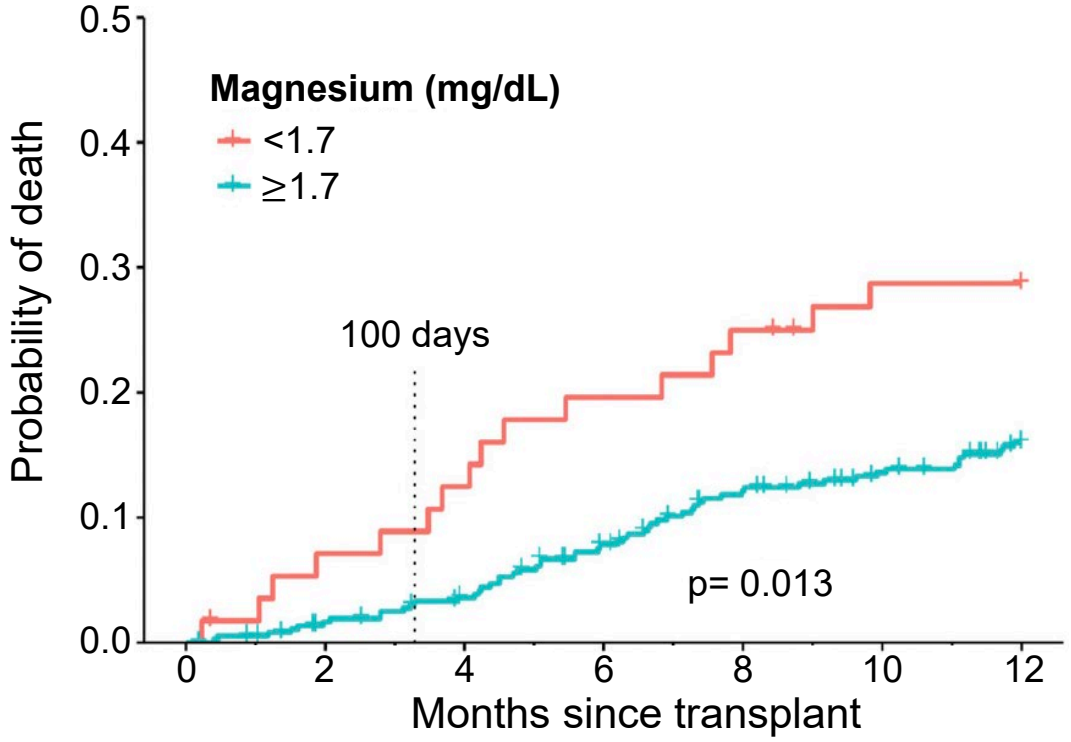
High Magnesium levels enhance immune response against tumor







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Gile JJ, et al Blood Cancer Journal 2021

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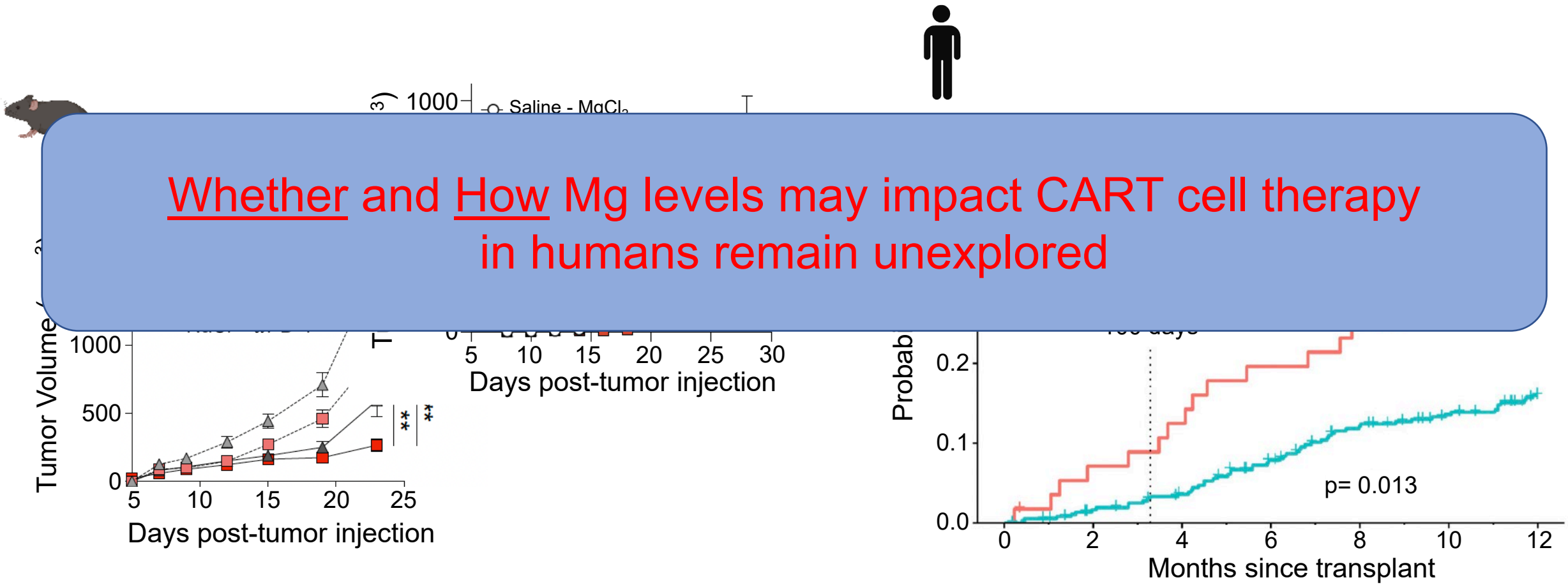

Lotscher, et al Cell 2022
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Methods

CLINICAL DATA

Discovery Cohort

- ZUMA-1 trial
  - 108 pts from cohort 1 (DLBCL) and 2 (PMBCL and tFL)[1,2]

Validation Cohort

- Mayo Clinic cohort
  - 57 LBCL pts s/p axi-cel between 2018-2020

- Low Mg^{2+}: < 1.7 mg/dL[3]
- Normal Mg^{2+}: ≥ 1.7 < 2 mg/dL
- High Mg^{2+}: ≥ 2 mg/dL[3]

BIOLOGIC ANALYSIS

Serum cytokine analysis (ZUMA-1:108 pts)

scRNA-seq of PBMCs (Mayo Clinic: 13 pts)

- Pre-CART (before lymphodepletion chemotherapy)
- CART-Peak

[1]Neelapu SS, et al NEJM 2017
[2]Locke FL, et al Lancet Oncol 2019
[3]Gile JJ, et al Blood Cancer Journal 2021

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Patient Characteristics

	ZUMA-1 (N= 108)				Mayo Clinic (N= 57)			
	Mg^{low} (N= 23)	Mg^{nl} (N= 48)	Mg^{high} (N= 37)	P value	Mg^{low} N = 12	Mg^{nl} N = 30	Mg^{high} N = 15	P value
Age				0.59				0.20
Median	56	57	59		61	57	60	
Male Sex	15 (65%)	30 (63%)	28 (76%)	0.42	6 (50%)	18 (60%)	10 (67%)	0.67
Diagnosis				0.18				0.14
DLBCL	19 (83%)	33 (69%)	32 (87%)		5 (42%)	22 (73%)	9 (60%)	
HG					4 (33%)	2 (7%)	1 (7%)	
PMBCL	0 (0%)	6 (13%)	2 (5%)		0 (0%)	0 (0%)	1 (7%)	
tFL	4 (17%)	9 (19%)	3 (8%)		3 (25%)	6 (20%)	4 (27%)	
ECOG PS ≥1	16 (70%)	32 (67%)	14 (38%)	**0.01**	6 (50%)	11 (37%)	6 (40%)	0.72
Elevated LDH	22 (96%)	39 (81%)	32 (87%)	0.26	9 (75%)	19 (63%)	10 (67%)	0.87
IPI	12 (52.2%)	20 (41.7%)	17 (45.9%)	0.71	9 (75%)	13 (43%)	9 (60%)	0.18
Stage 3/4	19 (82.6%)	37 (77.1%)	34 (91.9%)	0.19	12 (100%)	27 (90%)	15 (100%)	0.41
Prior Lines of Therapy				0.426				0.25
Median	4	3	3		3.5	3	3.0	
Range	1 - 10	1 - 8	2 - 6		3 – 5	1 – 6	2 – 5	
Prior ASCT	6 (26%)	13 (27%)	10 (27%)	>0.99	6 (50%)	14 (47%)	5 (33%)	0.68

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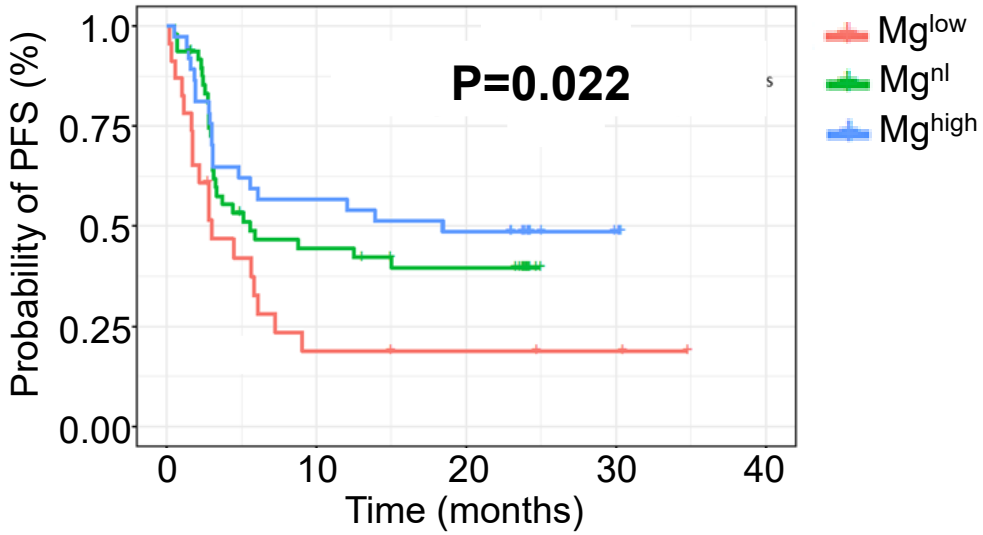
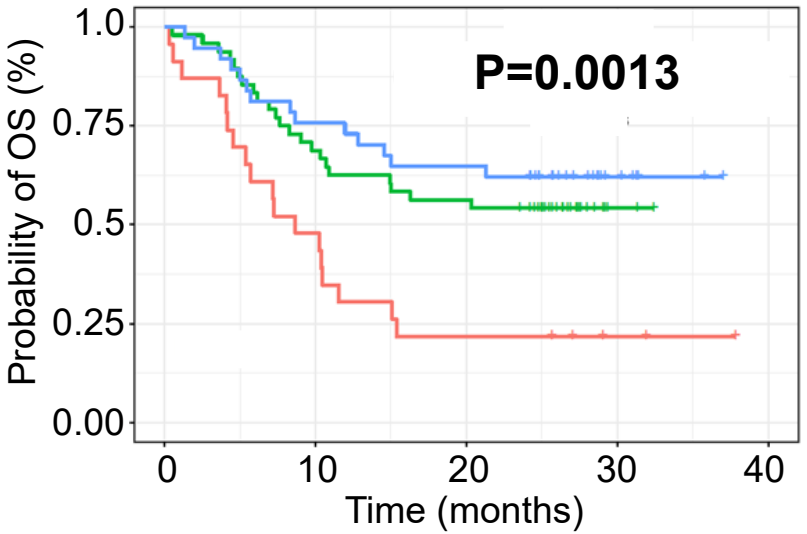
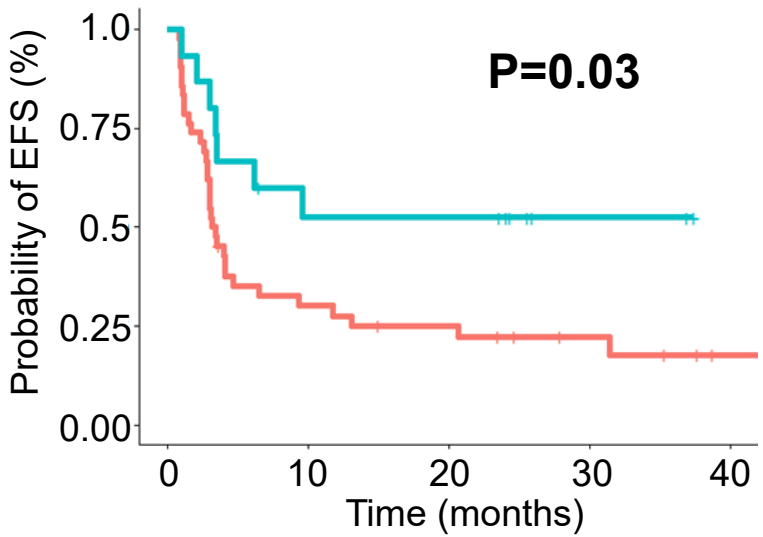
Hypomagnesemia impacts response and survival in LBCL patients treated with Axi-cel

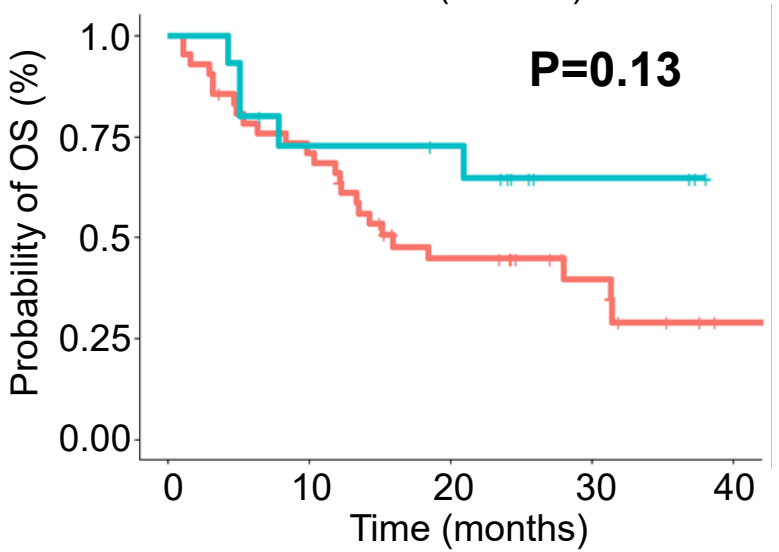
ZUMA-1





Mayo Clinic





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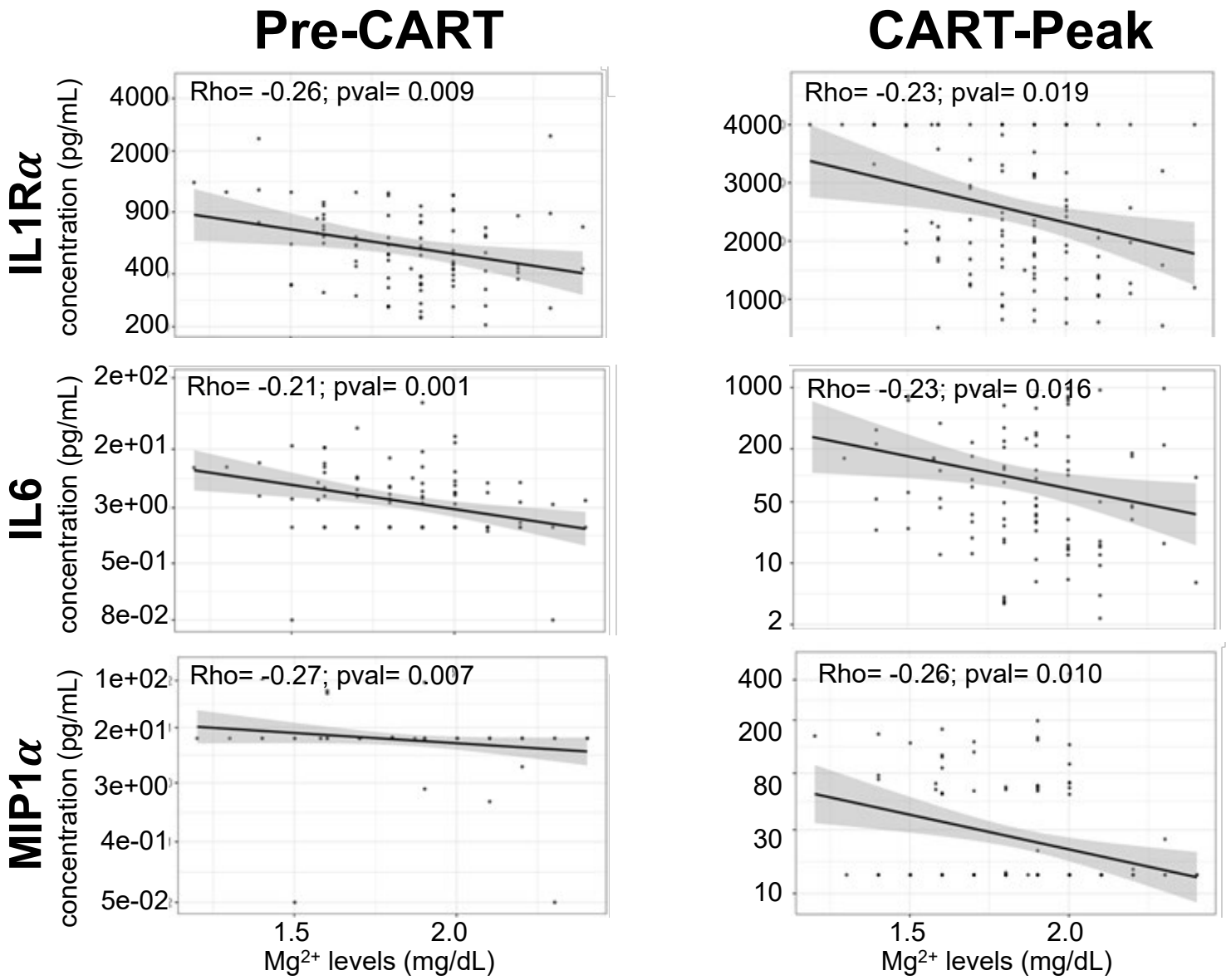
Hypomagnesemia inversely correlates with Interleukin levels and attenuates Immune effector cell-associated toxicity



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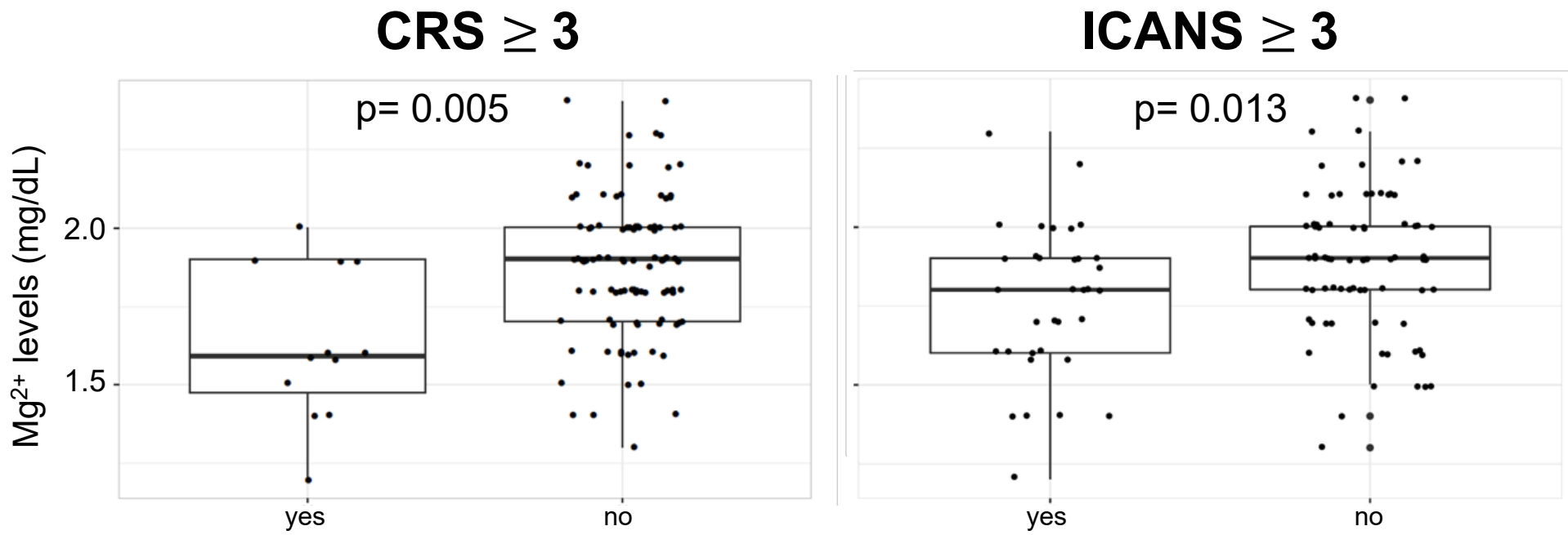

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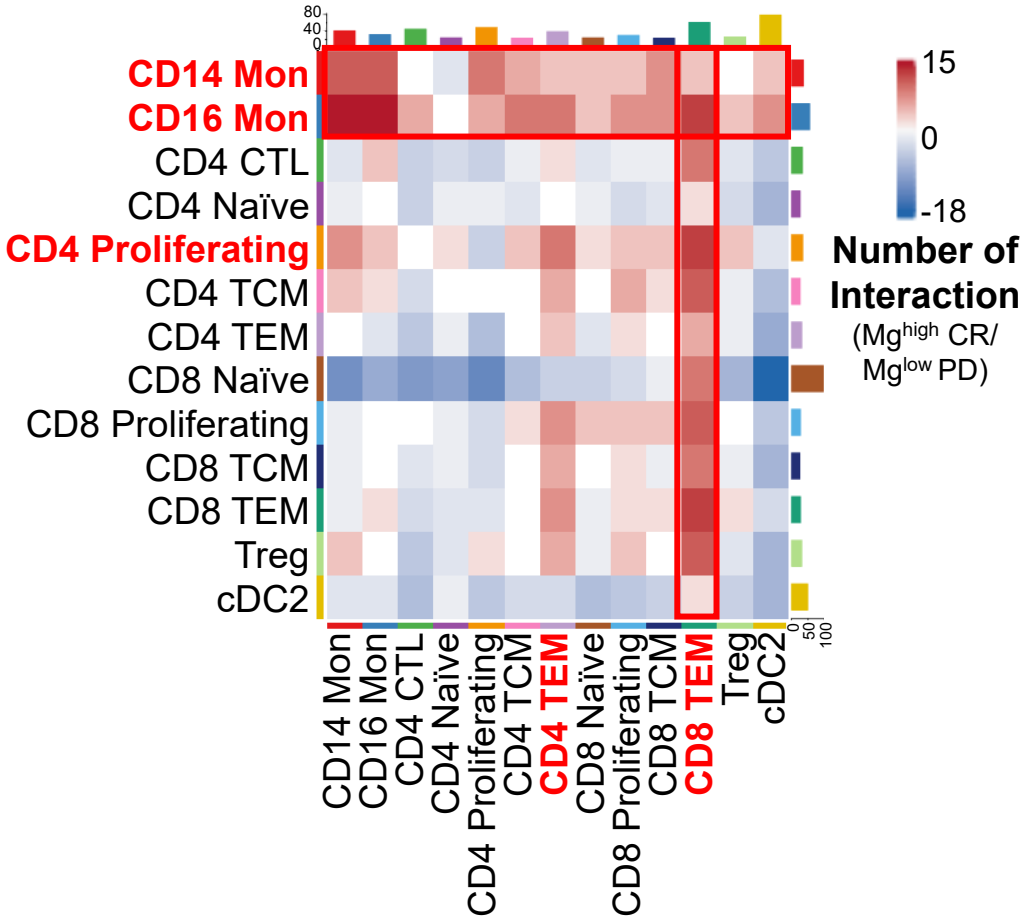
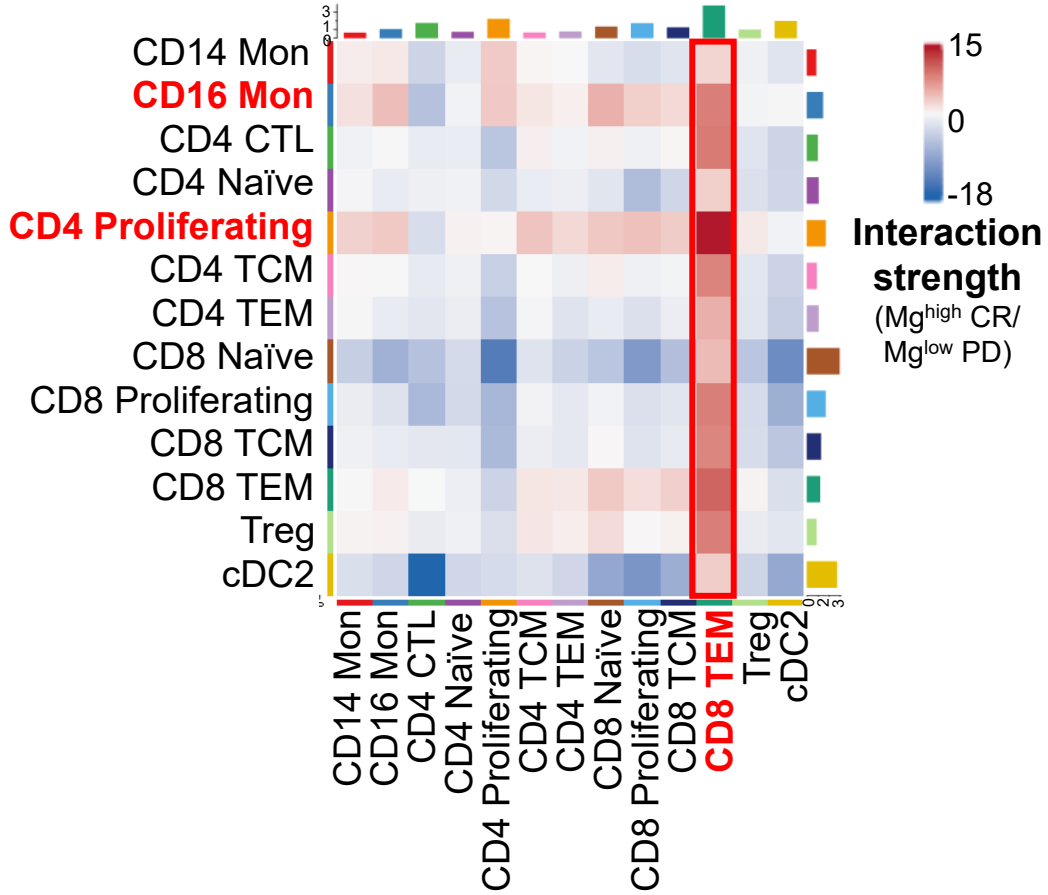
High magnesium at Pre-CART enhances immune interactions and clinical response





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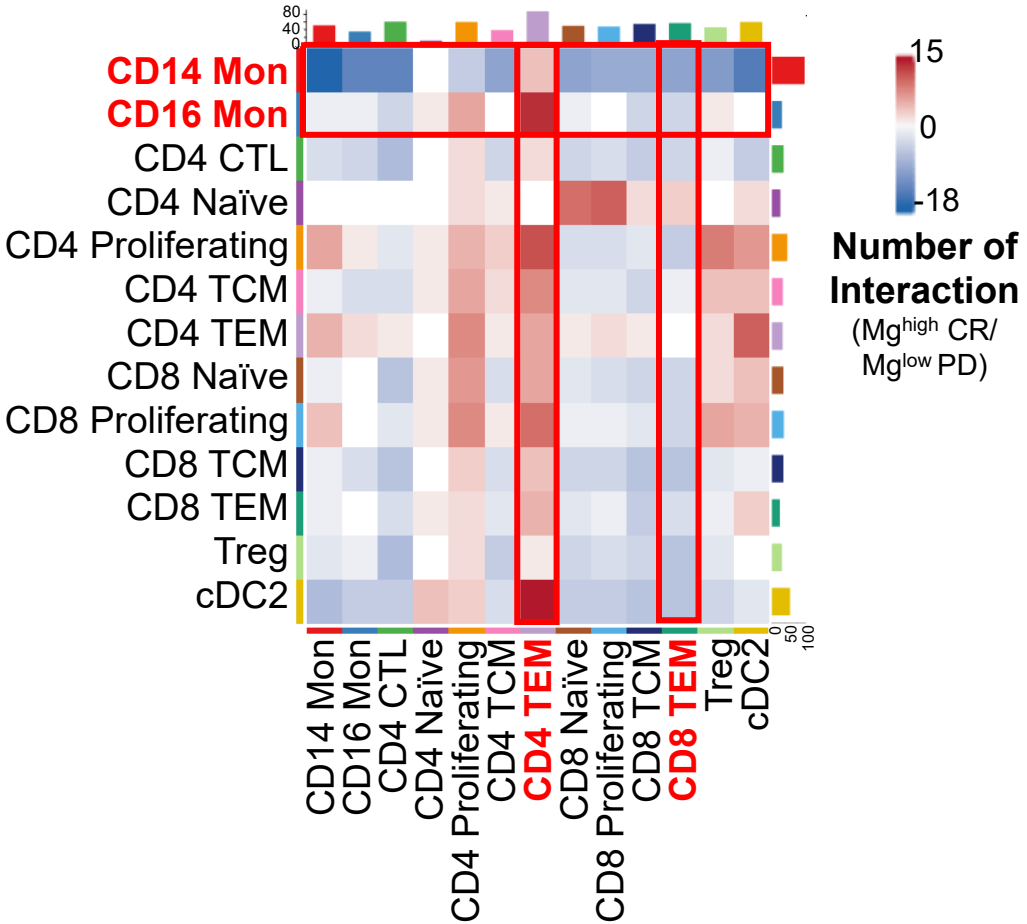
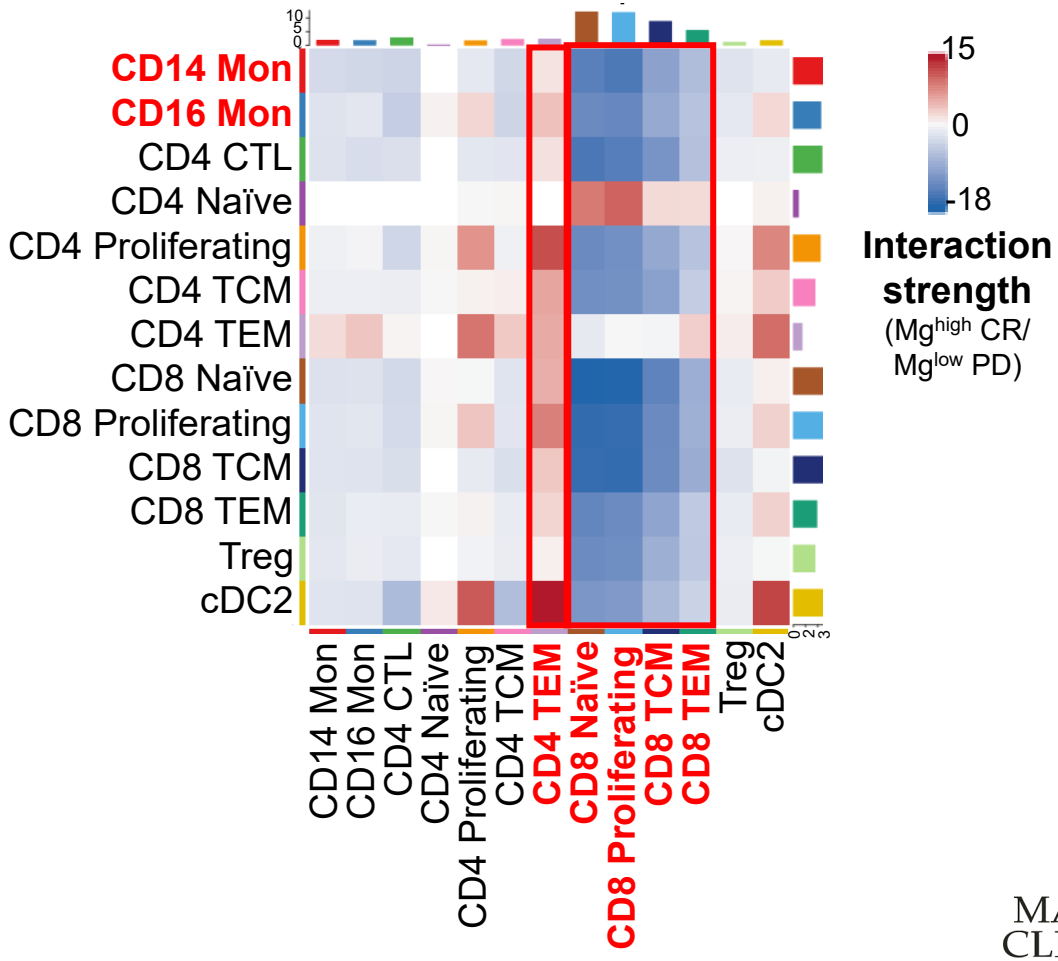
High magnesium at CART-Peak downregulates CD8 T cells while enhancing CD4 Effector Memory T cells





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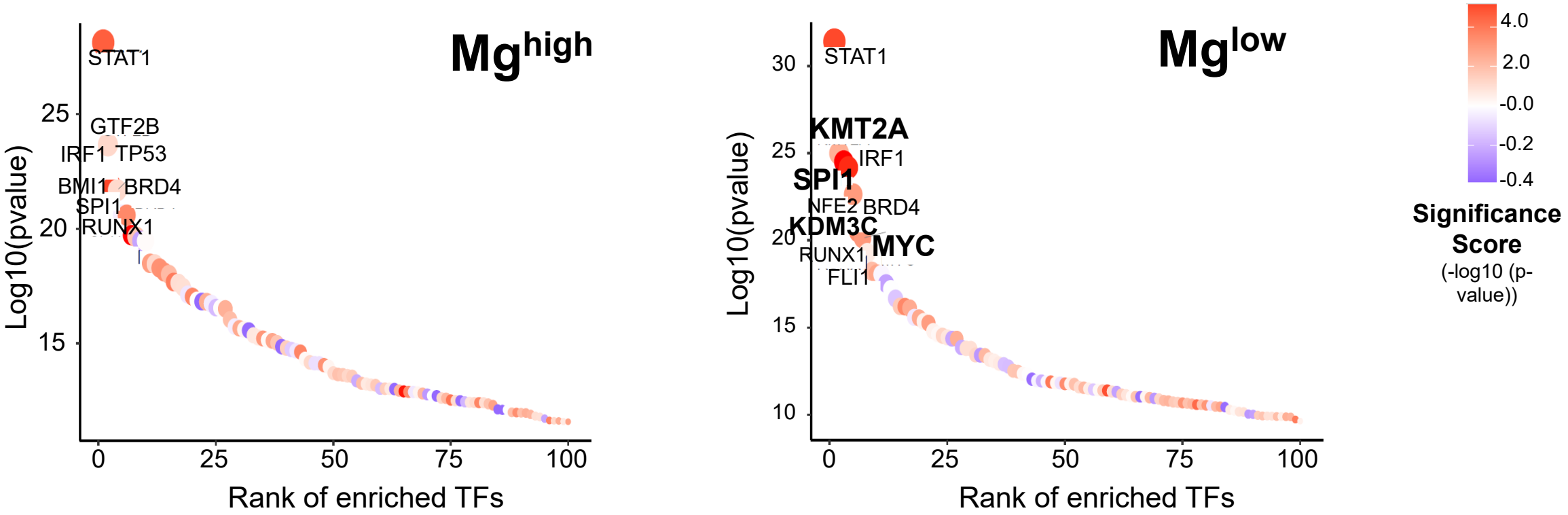
Hypomagnesemia induces transcriptional reprogramming



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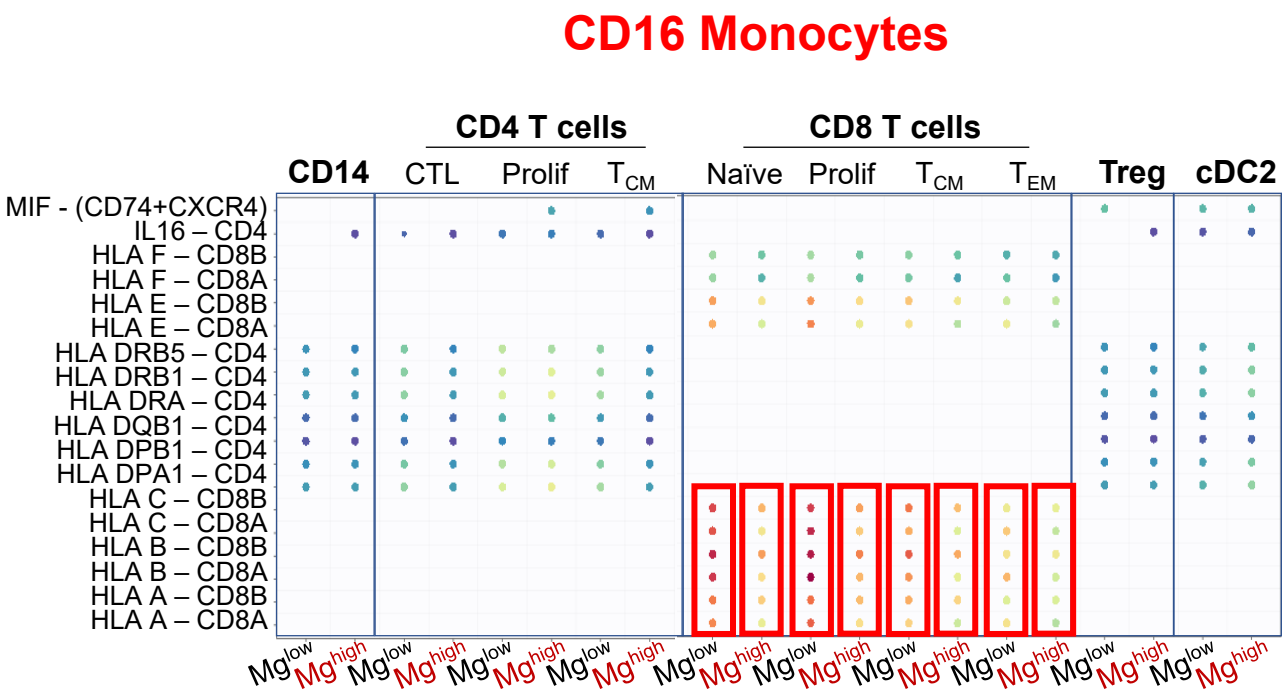
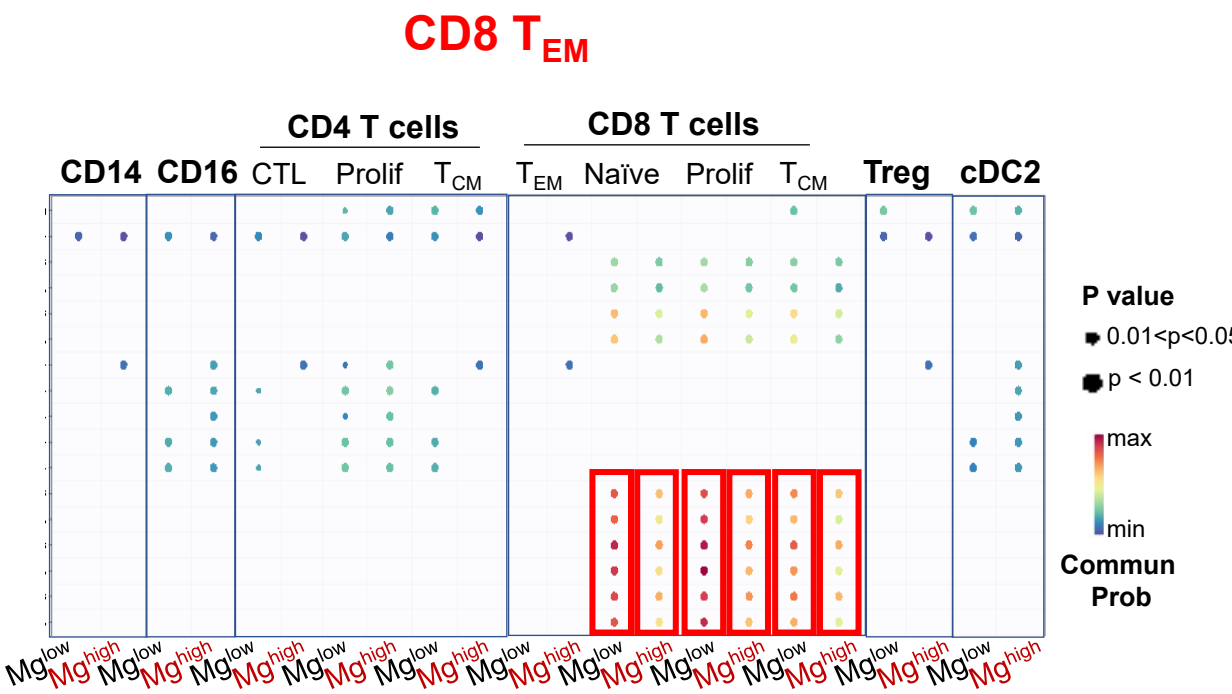
Magnesium levels modulate ligand-receptor interactions with potential ramification on CART efficacy





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Conclusions:

- Hypomagnesemia is prognostic in patients with LBCL receiving CART cells
- Mg^{2+} levels inversely correlate with interleukin levels before and after CART therapy and influence immune effector cell-associated toxicities
- Hypomagnesemia alters immune cell interactions (e.g. monocytes, CD4 and CD8 T cells)
- Optimization of Mg^{2+} levels may improve CART cells efficacy by enhancing immune response

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