1st Cuneo City Immunotherapy Conference (CCITC)

Immunotherapy in Hematological Malignancies 2018

CUNEO

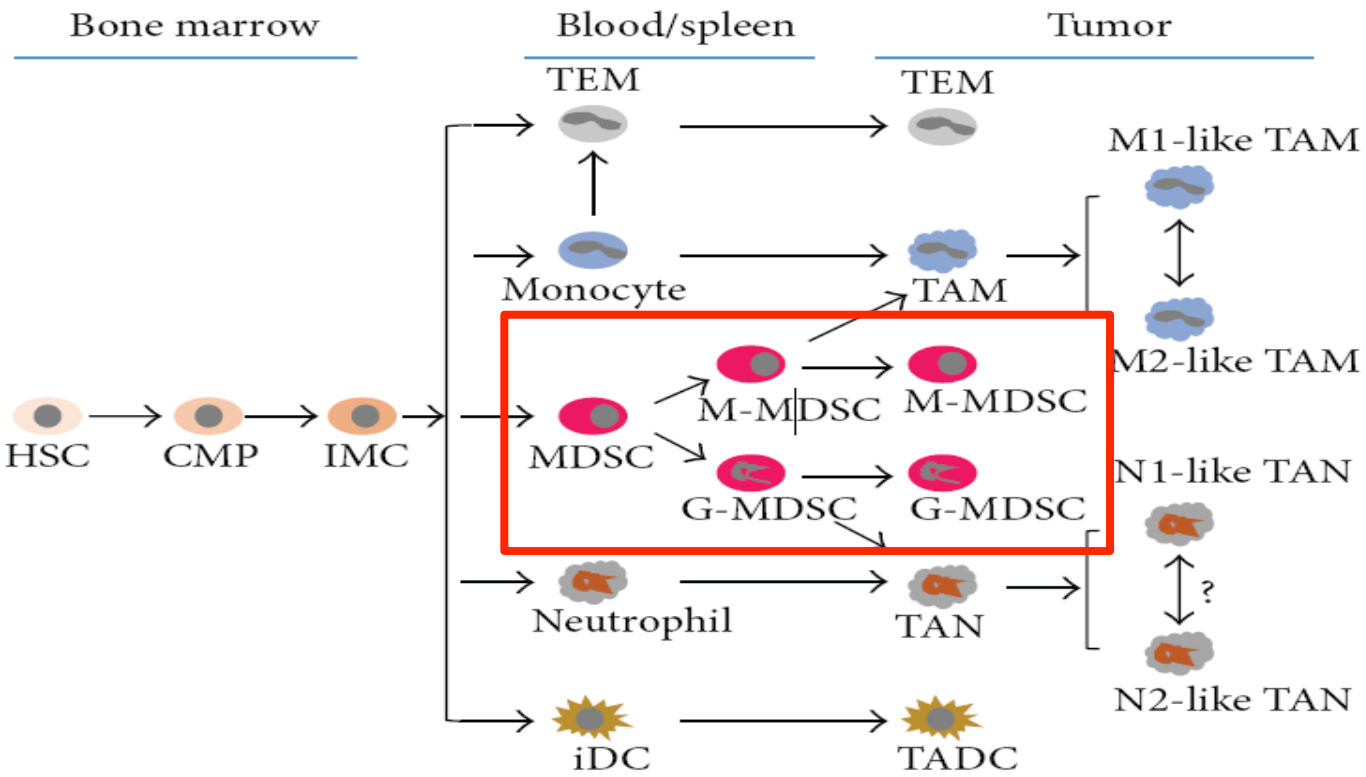
May 17-19, 2018

Centro Incontri

ROLE OF AMINOACIDS DEGRADING ENZYMES IN LYMPHO-PROLIFERATIVE DISEASES

FRANCESCO DI RAIMONDO
UNIVERSITY OF CATANIA

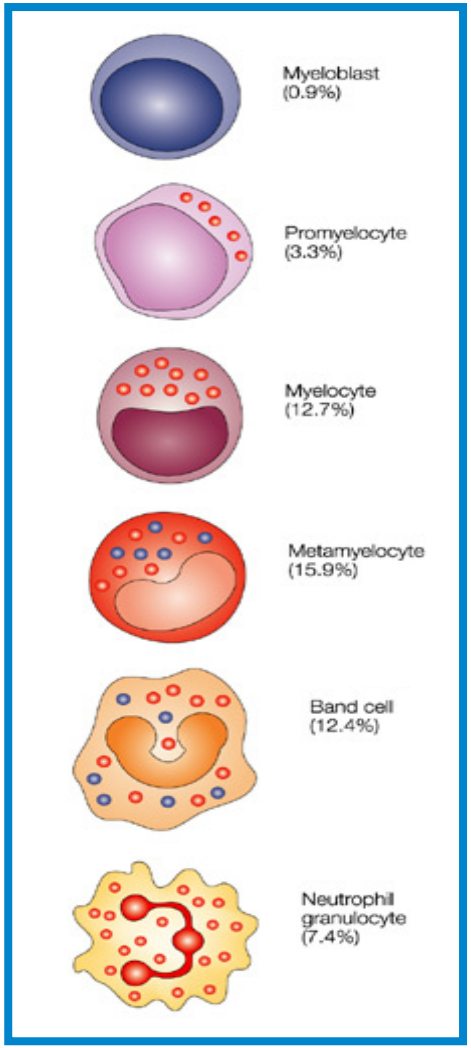
Tumor-associated myeloid cells



IMC: immature myeloid cells, TEM: Tie2-expressingmonocyte, MDSC:myeloid-derived suppressor cell, M-MDSC: myeloid MDSC, G-MDSC: granulocytic MDSC, iDC: immature dendritic cells, TADC: tumor-associated dendritic cells,TAM: tumor-associated macrophage, and TAN: tumor-associated neutrophil

Kim J, Med Inflam 2016

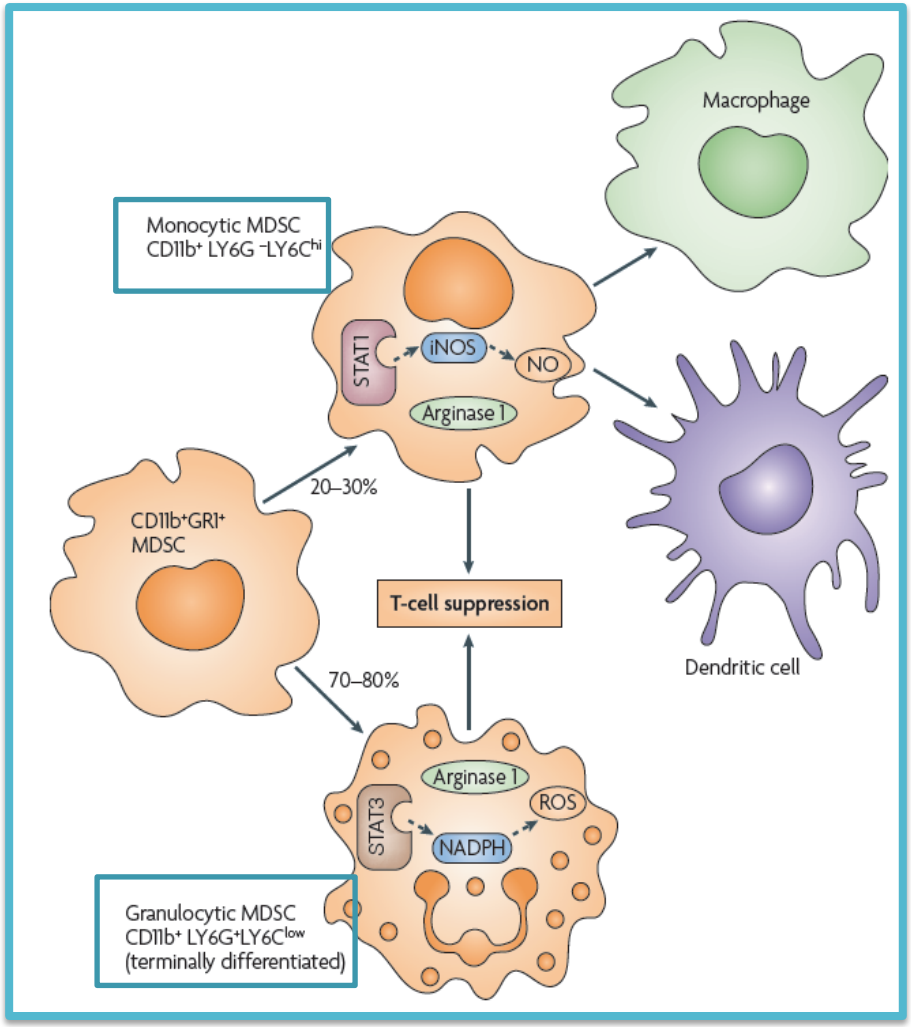
What myeloid-derived suppressor cells are



MDSC INDUCERS

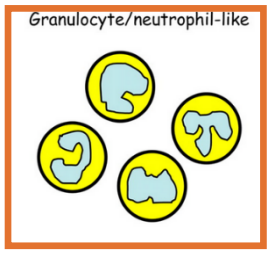
G-CSF, IL1-β,
IL-4, IL6,
TGF- β

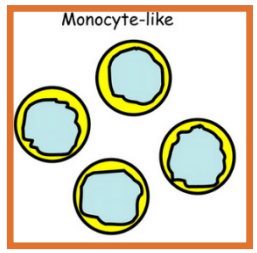
(e.g. inflammation, trauma, tumour)

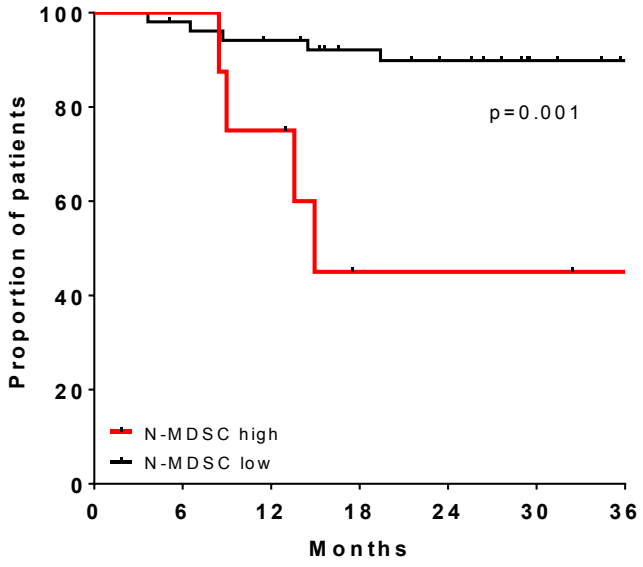


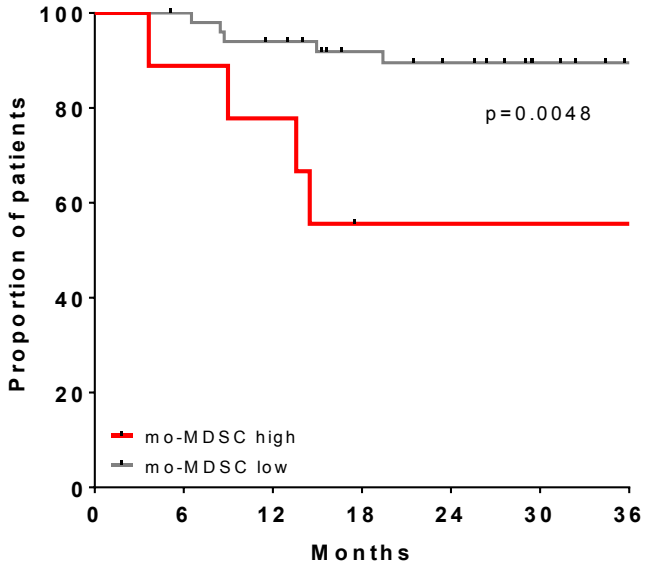
Gabrilovich et al; Nat Rev Immunol. 2009 Mar;9(3): 162-74.

MDSC and clinical outcome in HL



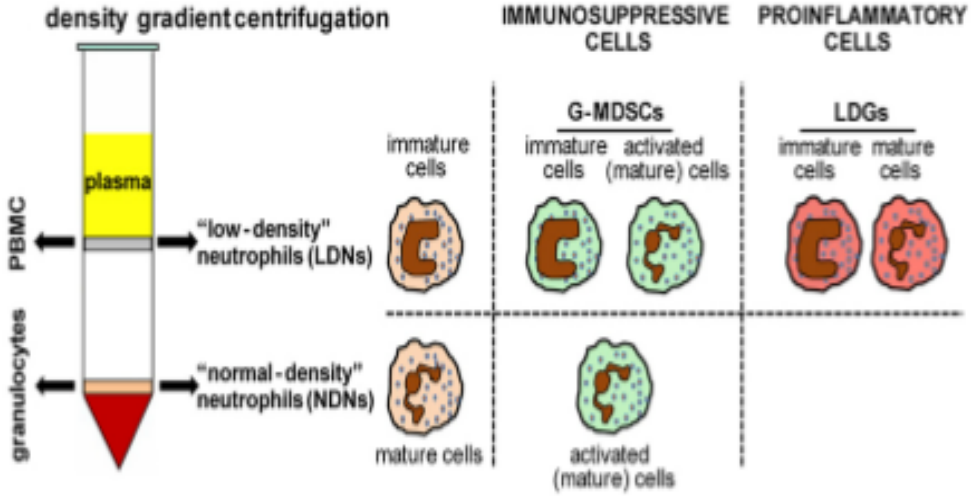


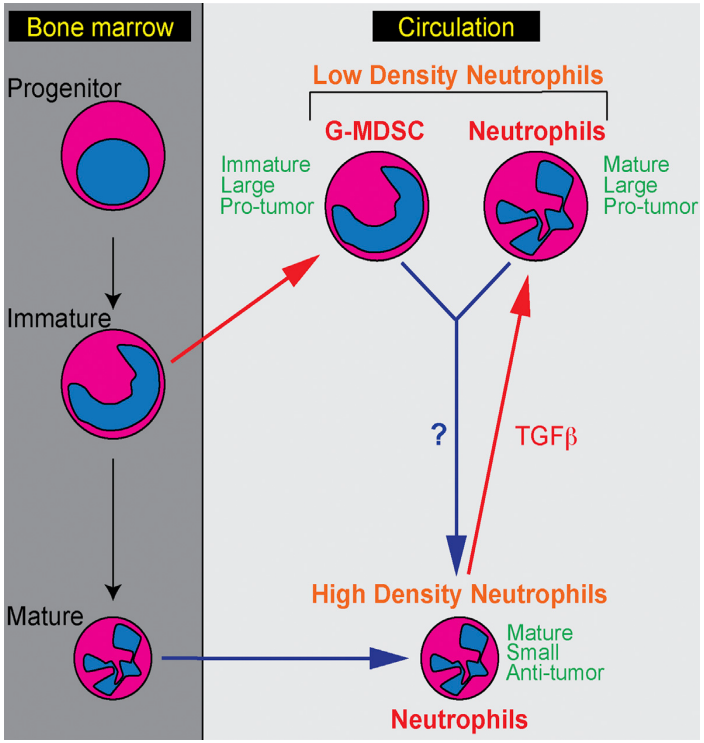




Romano A, BJH 2015

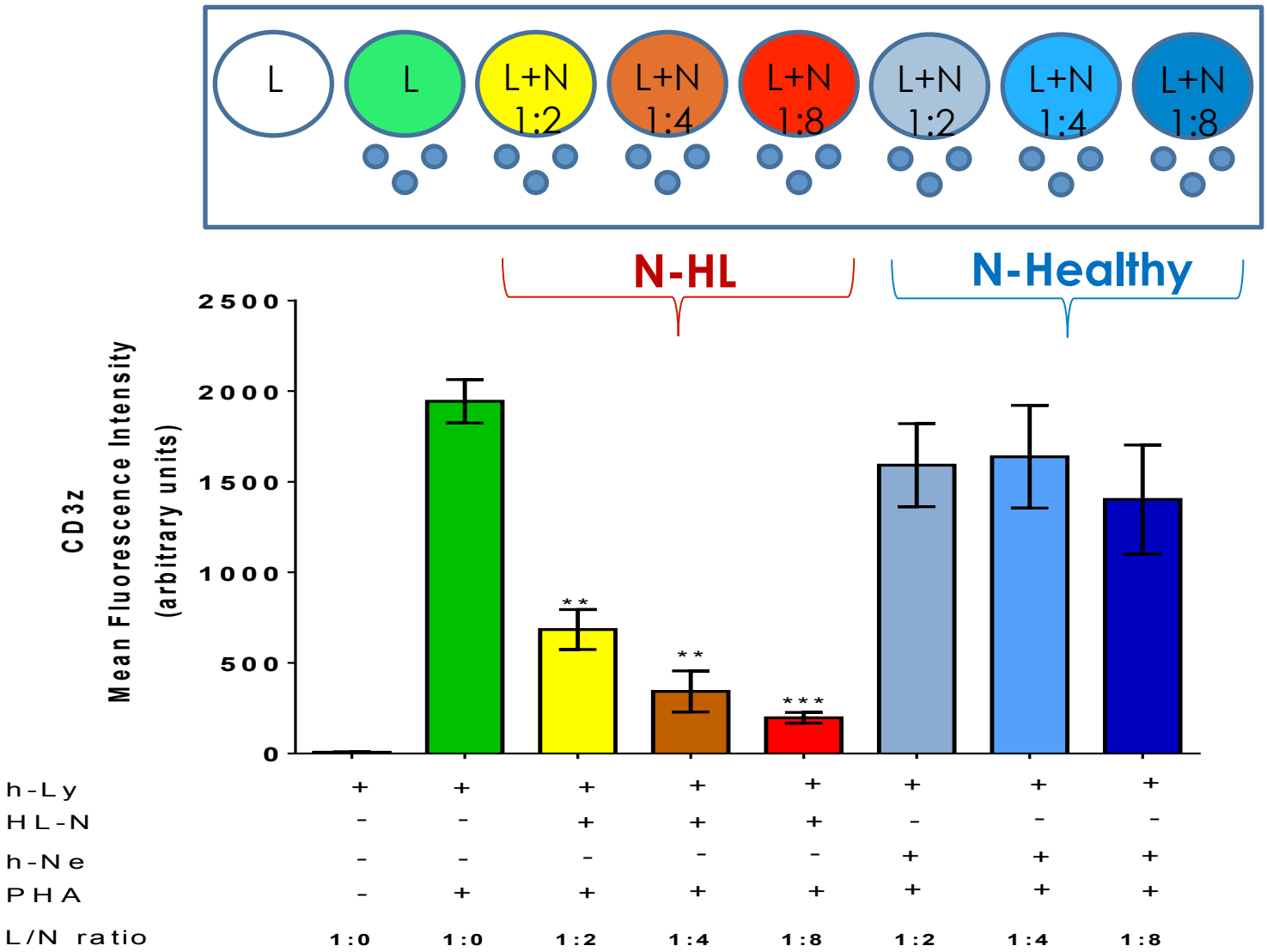
G-MDSC or low-density neutrophils in peripheral blood?



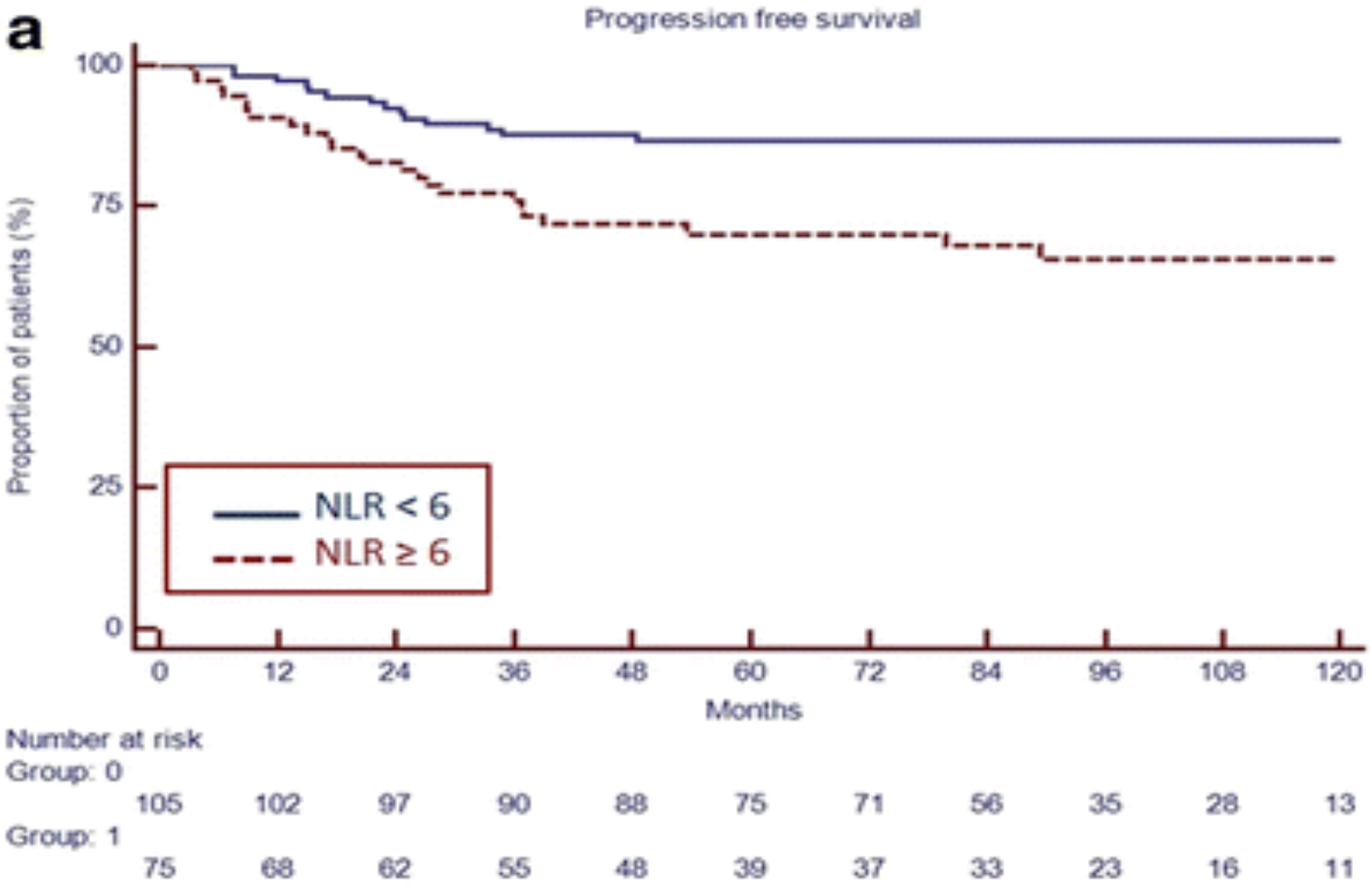


Sagiv et al., Cell Reports 2015

N-HL: functional evaluation

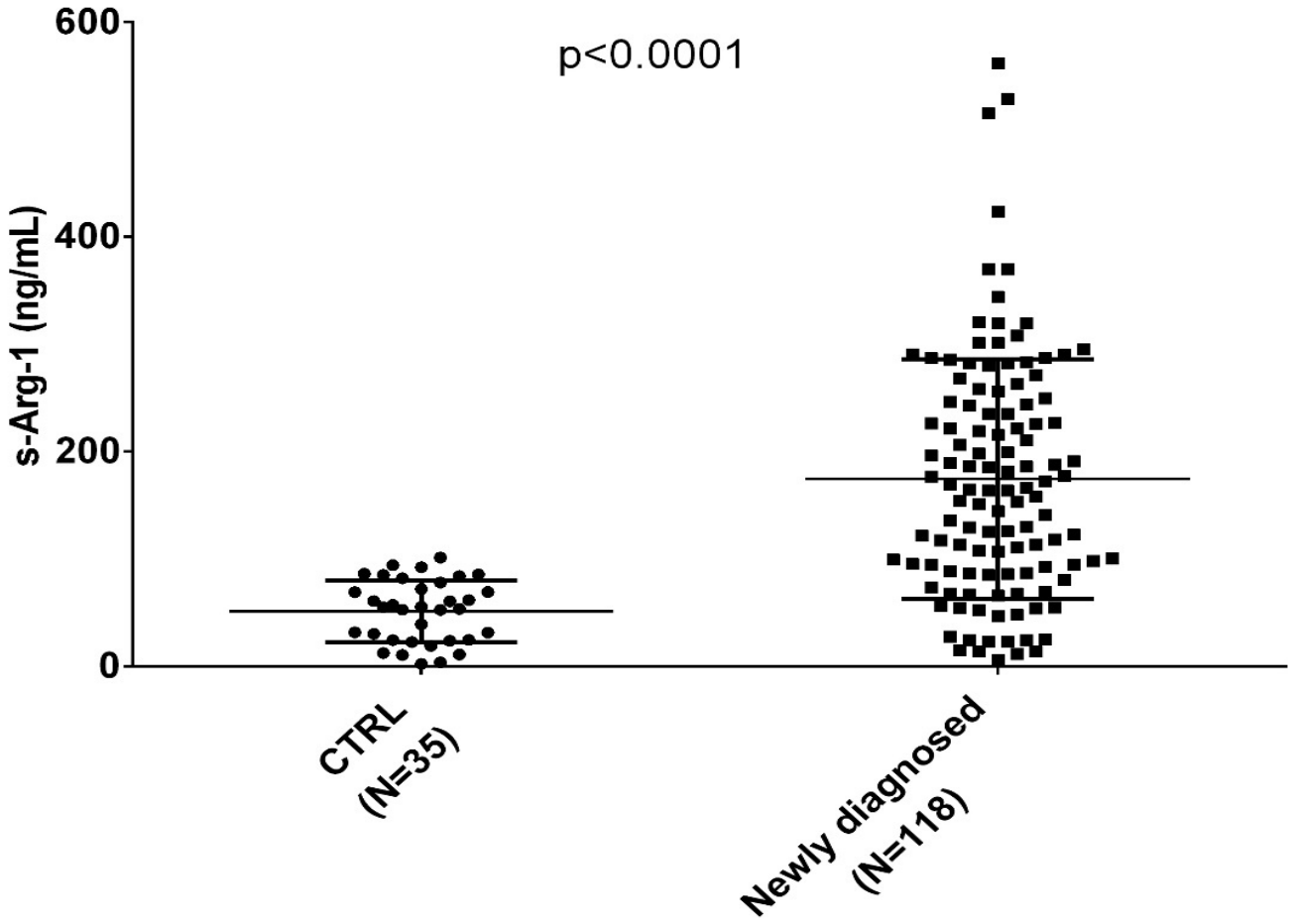


NLR in Hodgkin Lymphoma



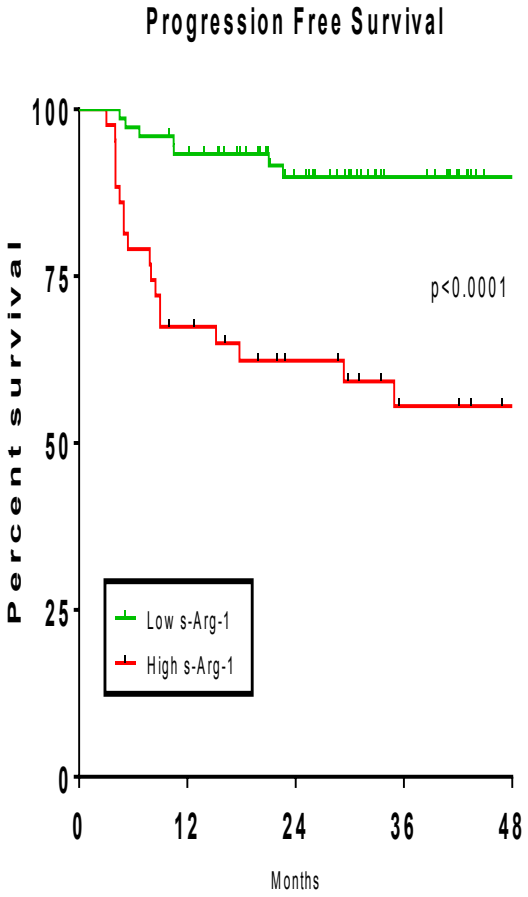
Romano A, Ann Hematol 2018

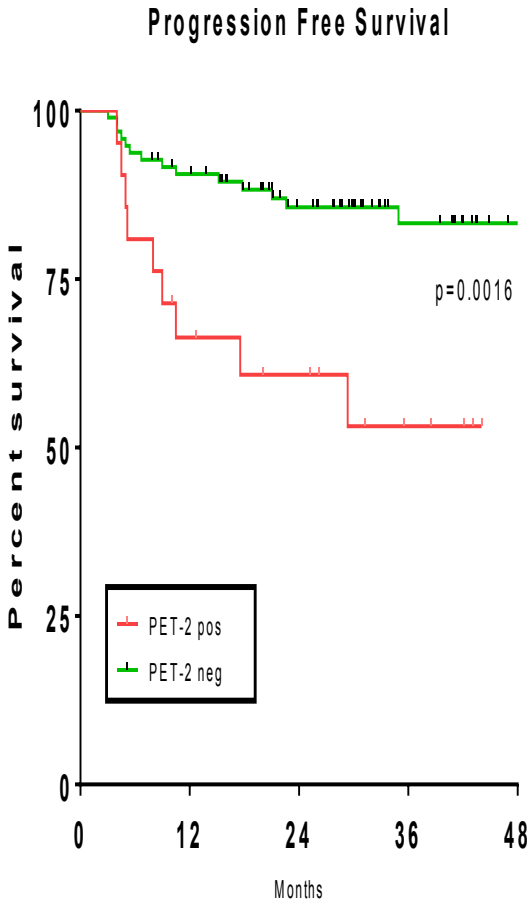
S-Arg-1 is increased in HL

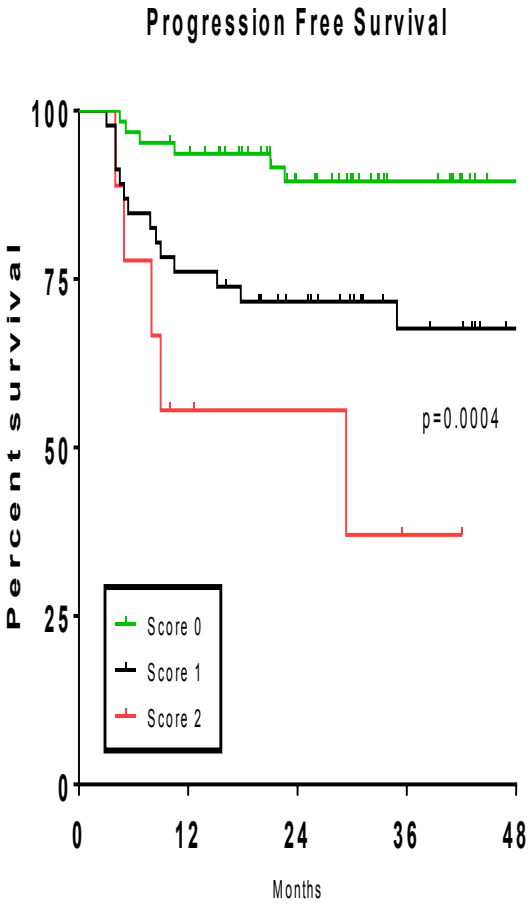


Romano A, Oncotarget 2016

S-Arg-1 and PFS (n=118)



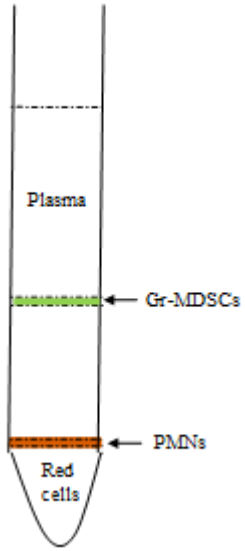


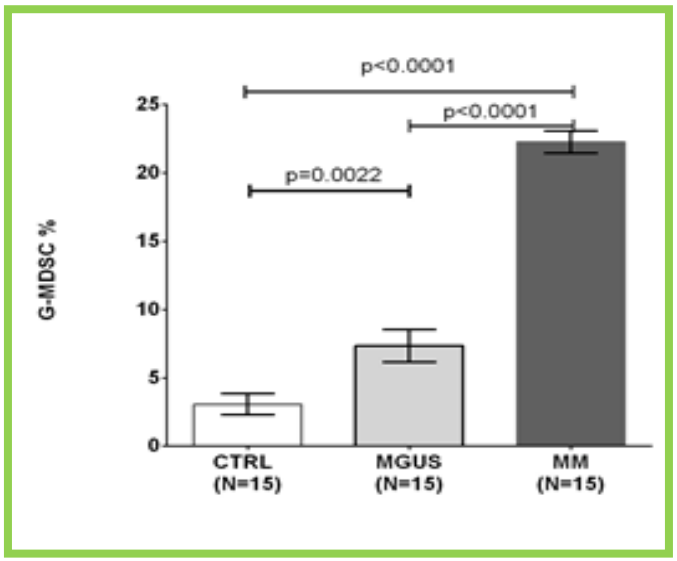


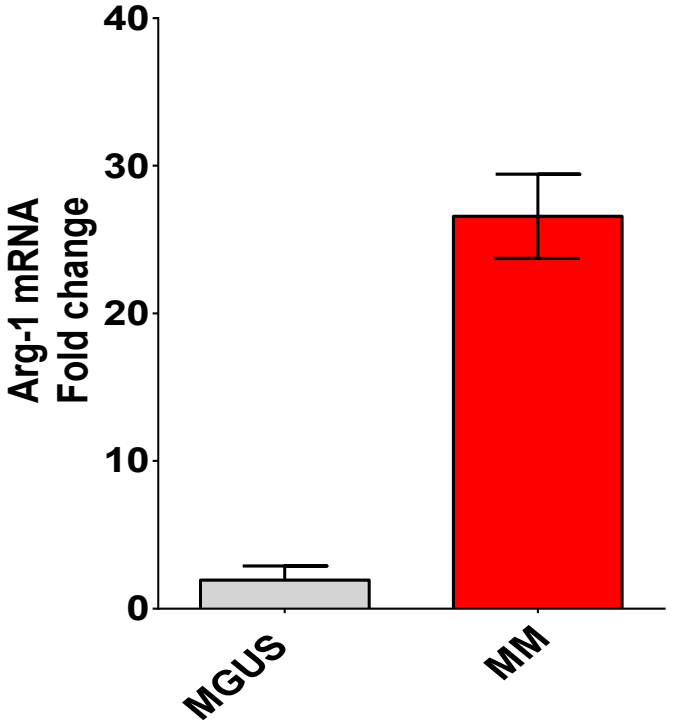
Romano A, Oncotarget 2016

G-MDSCs sono aumentate nel MM

Ficoll upper ring

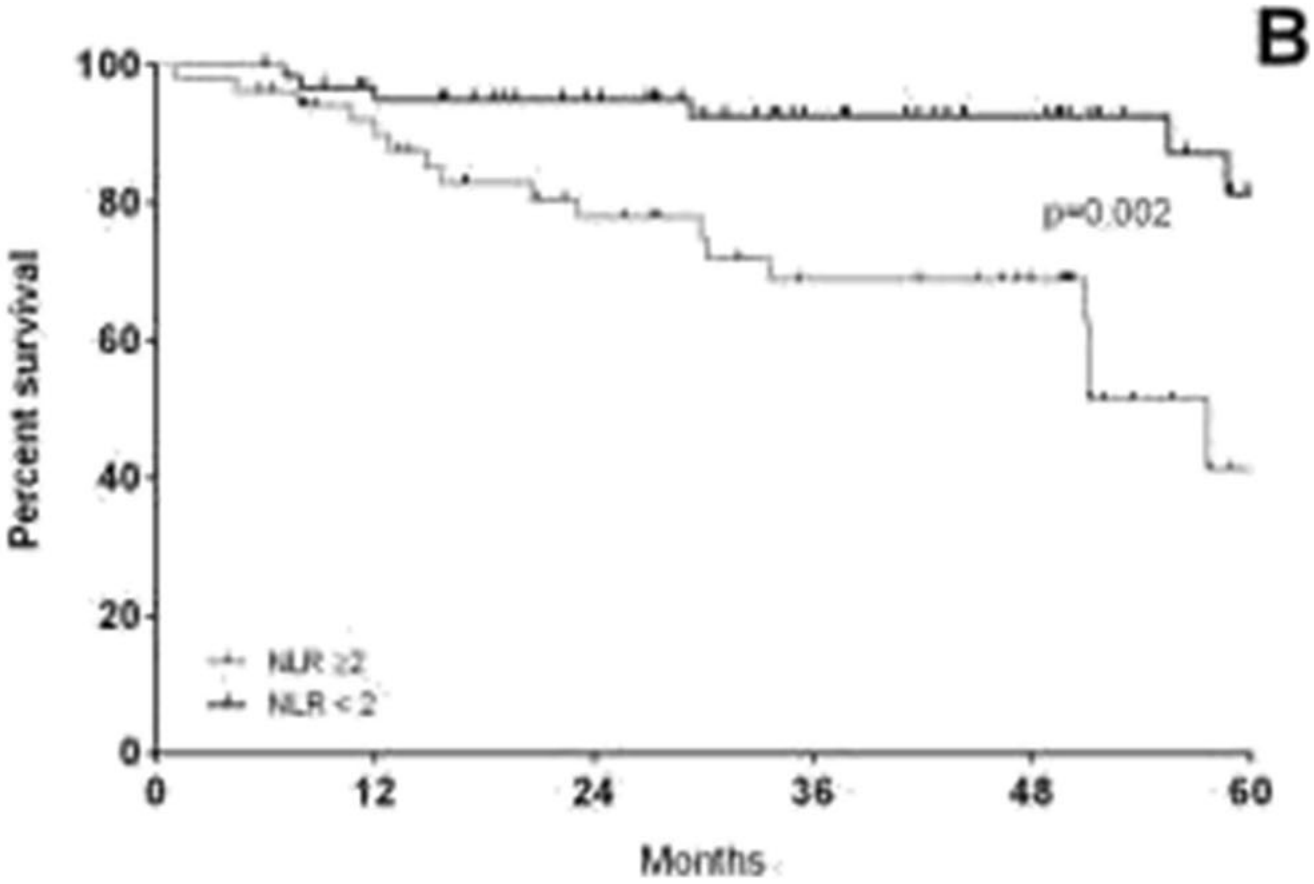






Romano A.,Parrinello N., manuscript under revision

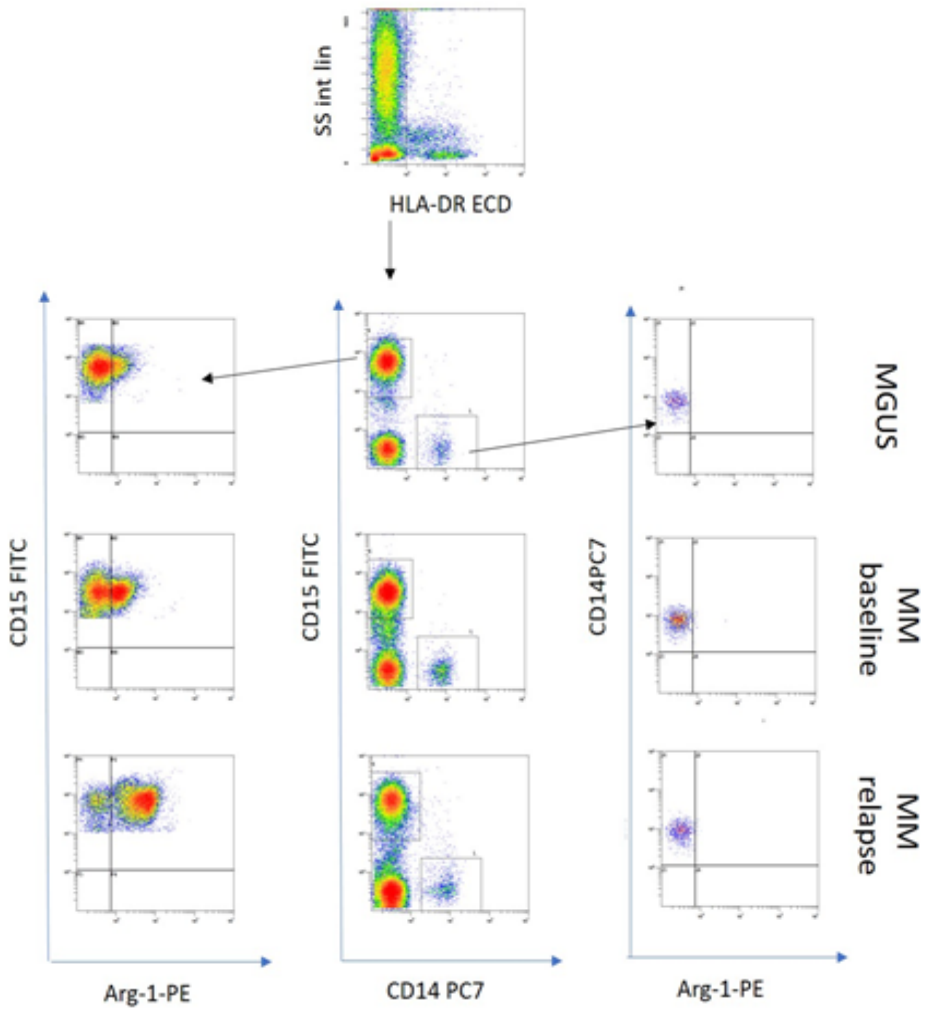
Significance of NLR in Myeloma Patients Treated with ABMT

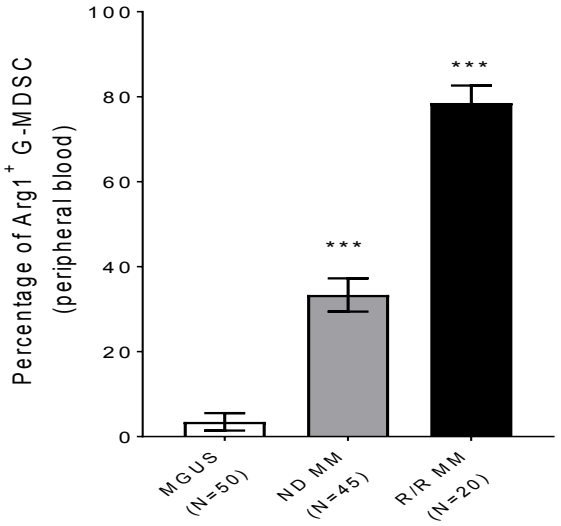


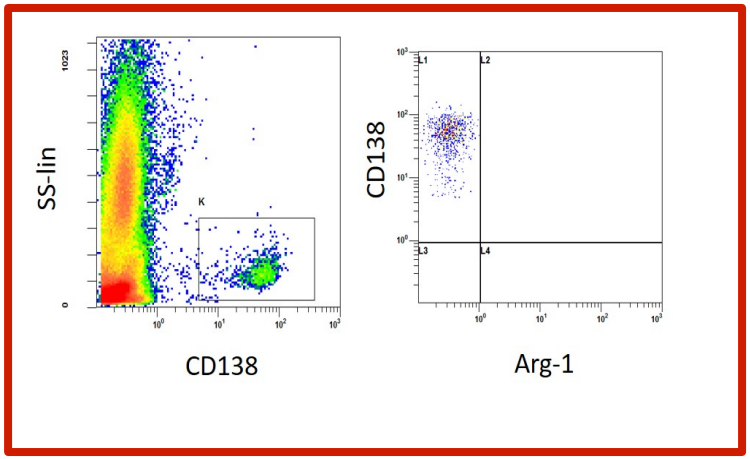
Romano A, Ann Hematol 2015

Arg-1 is increased in MM-G-MDSC

myeloid but not MM cells express aminoacid degrading enzymes Arg-1

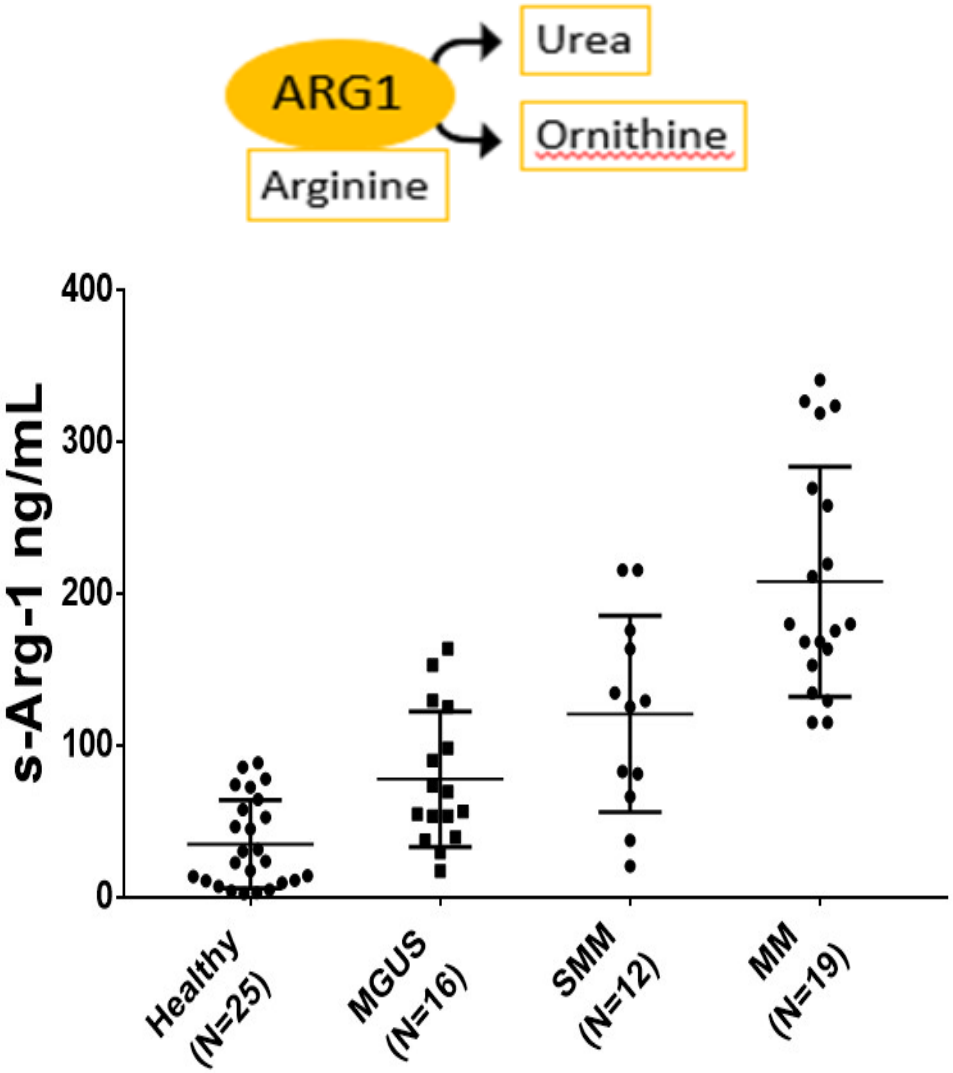


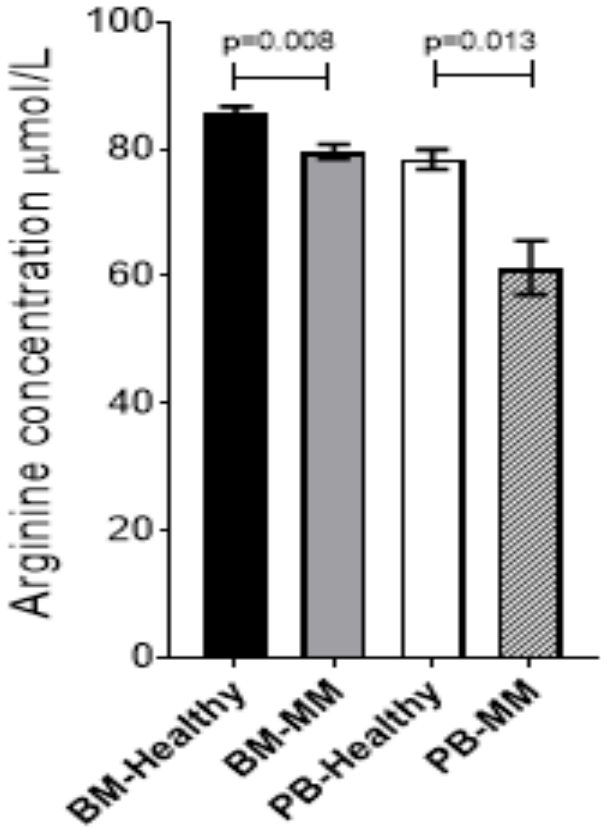




Romano, Ex.Rev.Hem, 2018

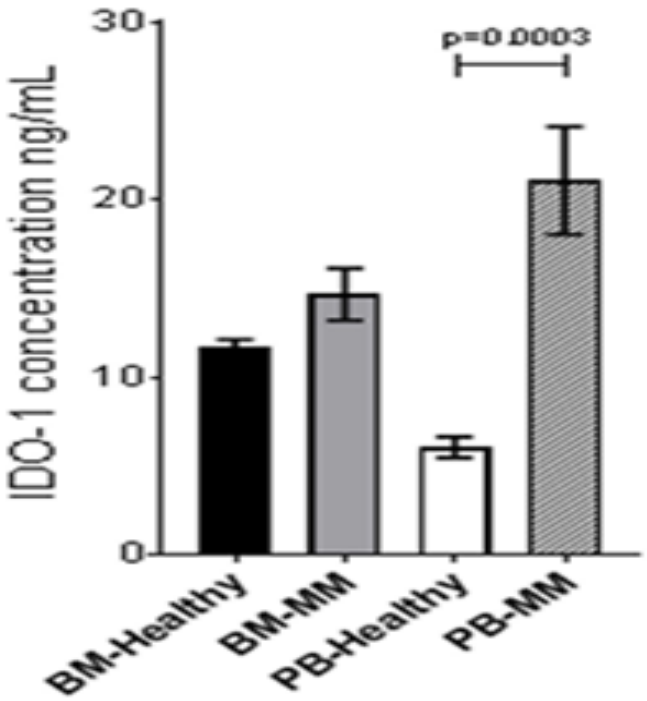
Aminoacid shortage in MM environment

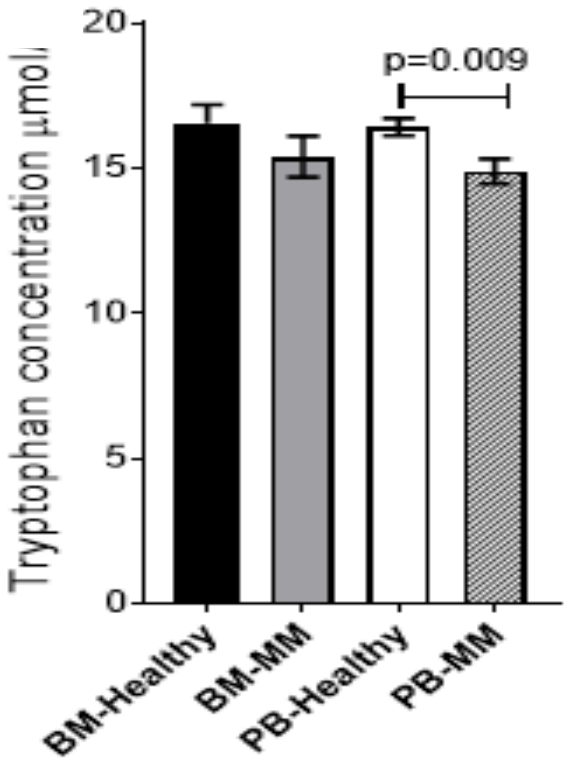




La Cava and Romano, unpublished data

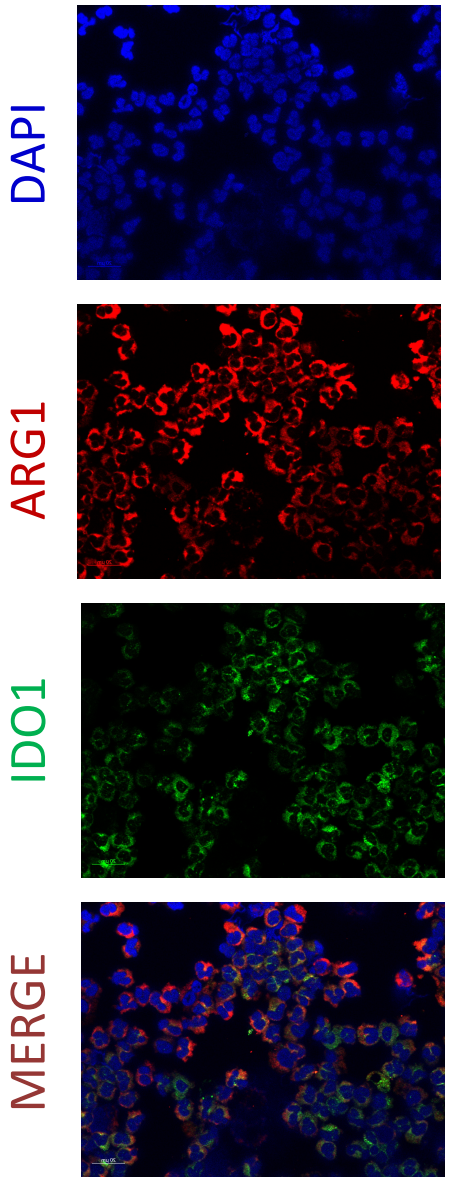
Aminoacid shortage in MM environment

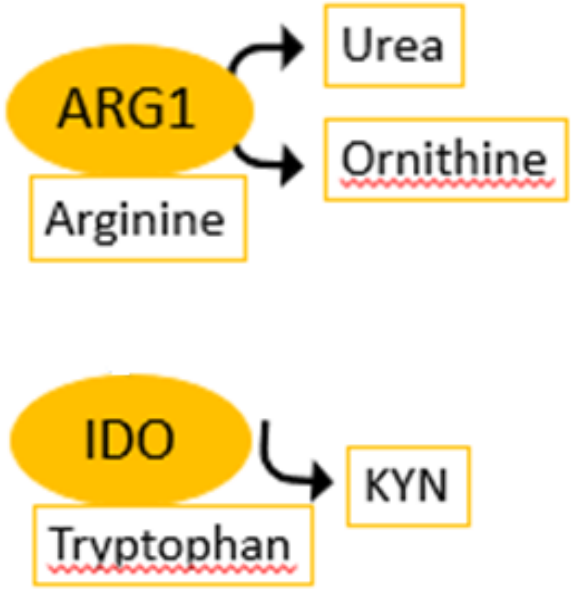


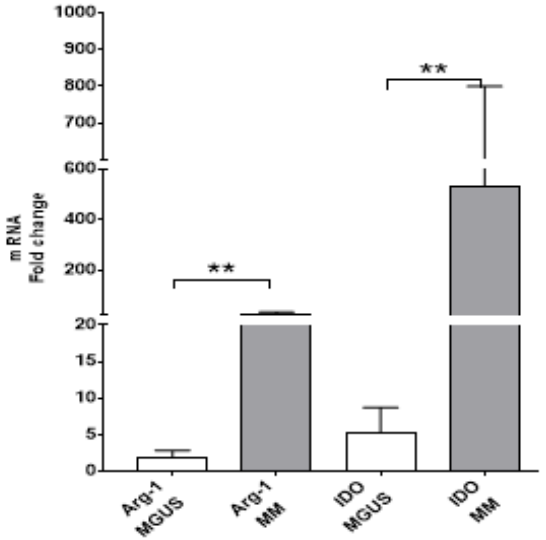


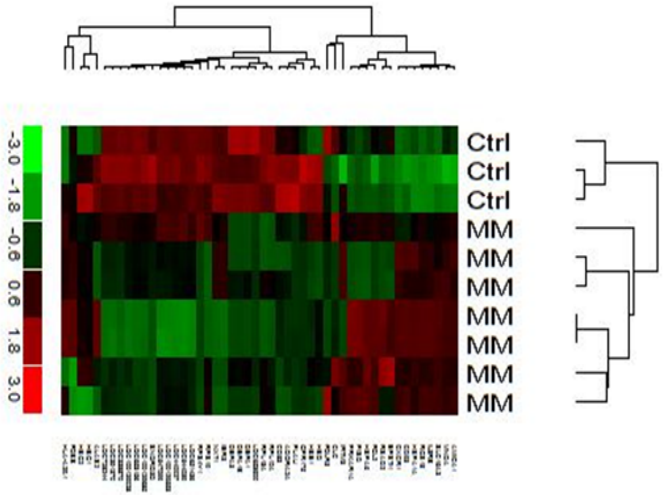
La Cava and Romano, unpublished data

Aminoacid degrading enzymes are increased in HDN-MM

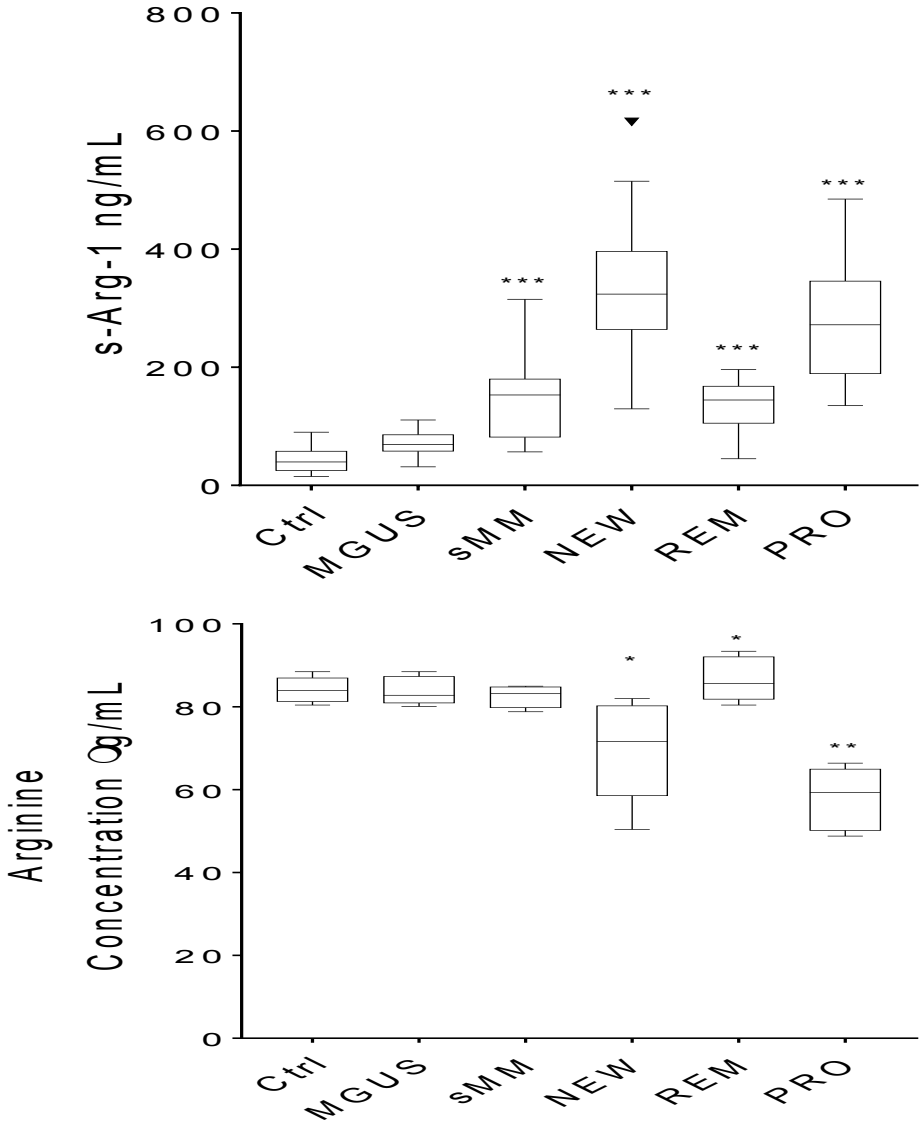


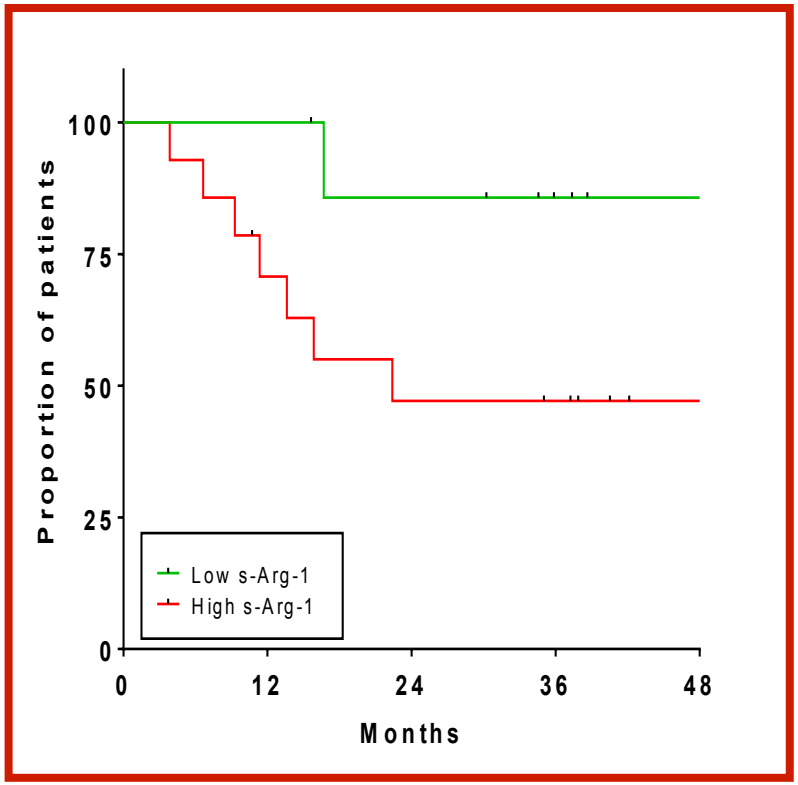






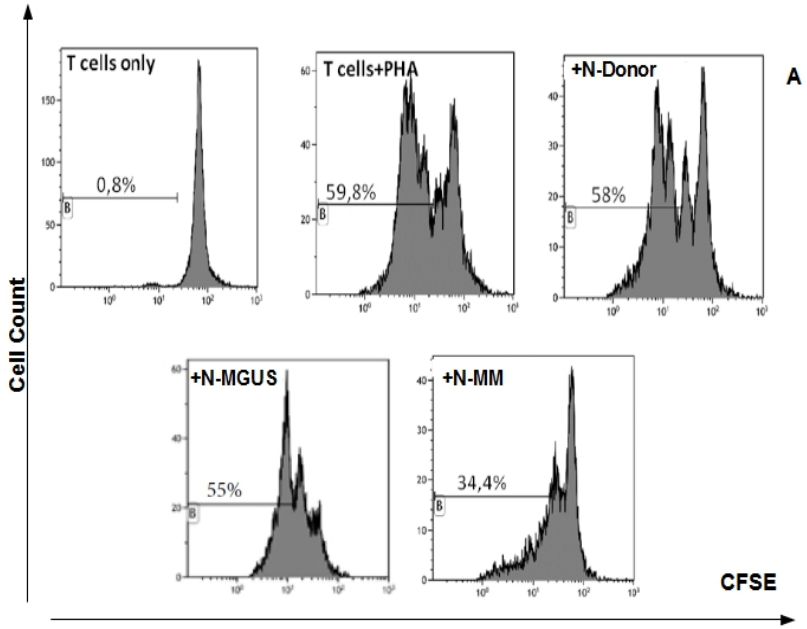
Increased Arg-1 and reduced arginine in MM

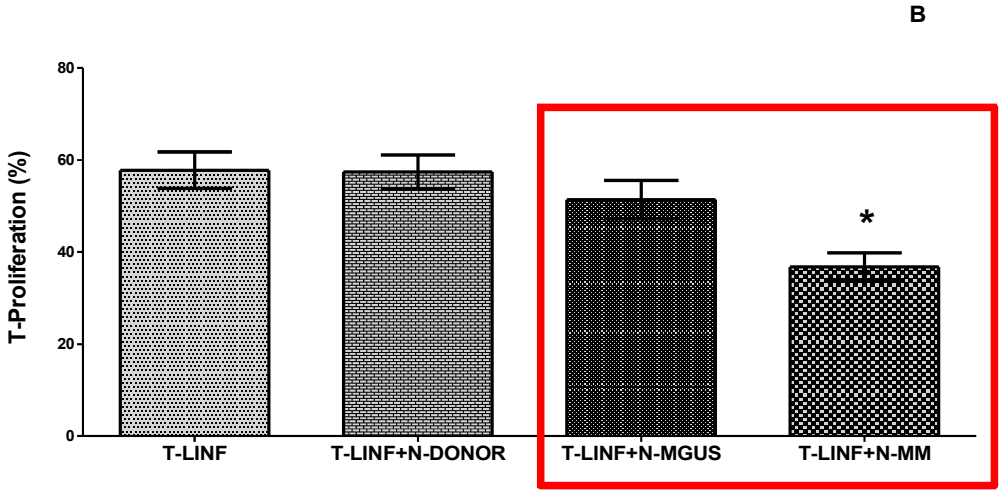




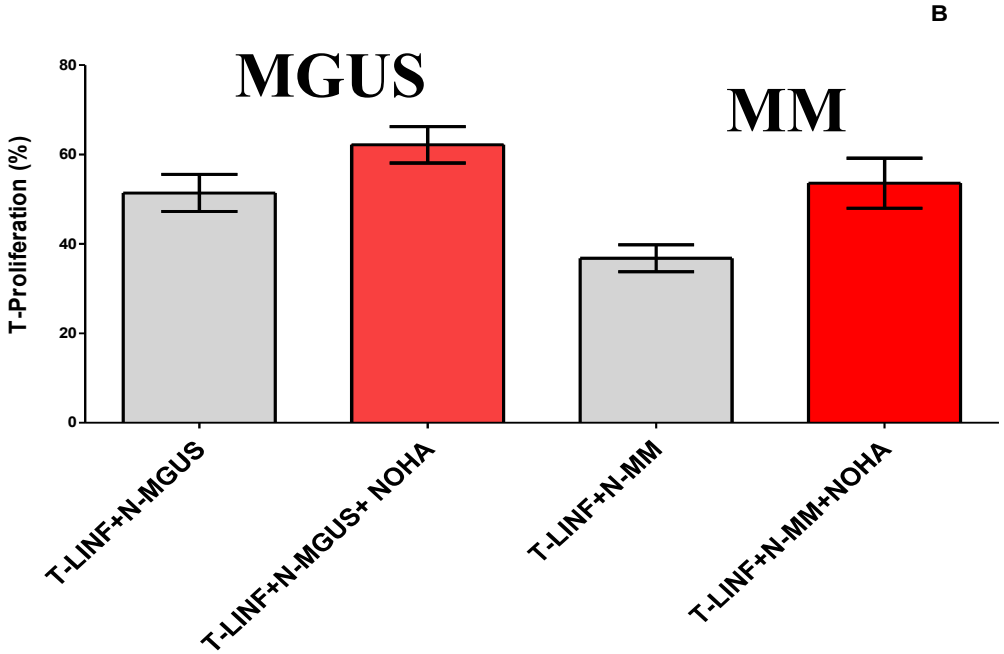
La Cava and Romano, unpublished data

Neutrofili di MM inibiscono la proliferazone T-cellulare

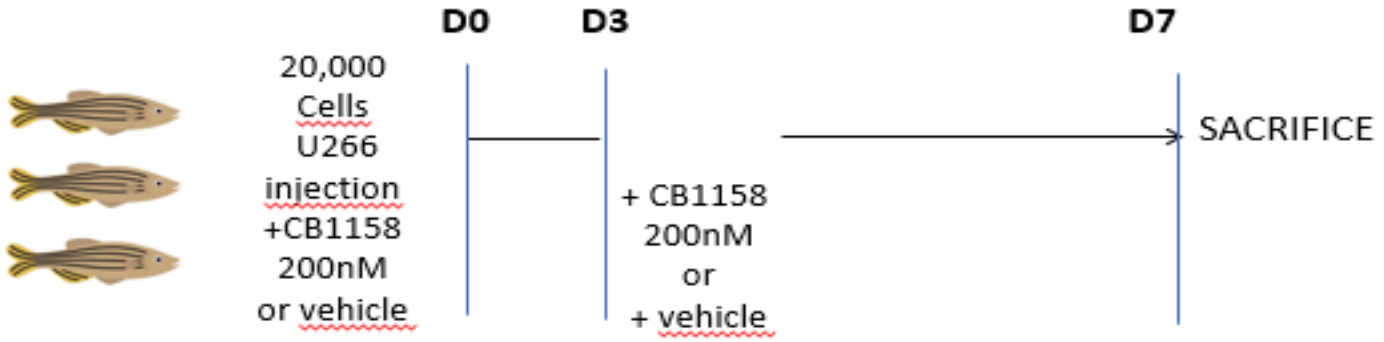


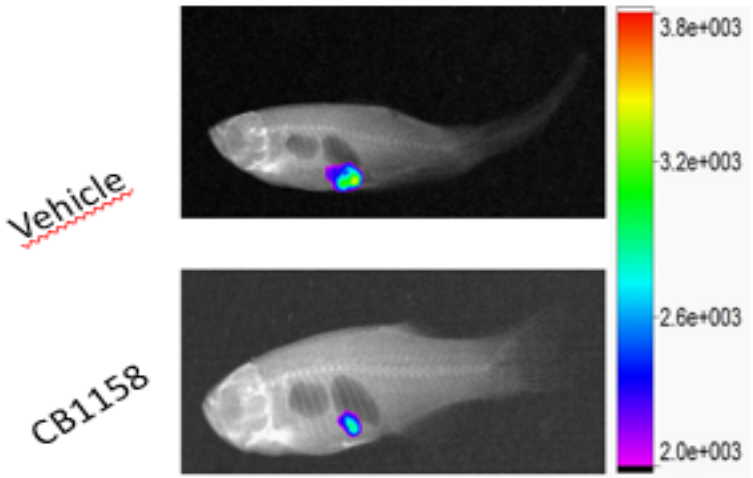


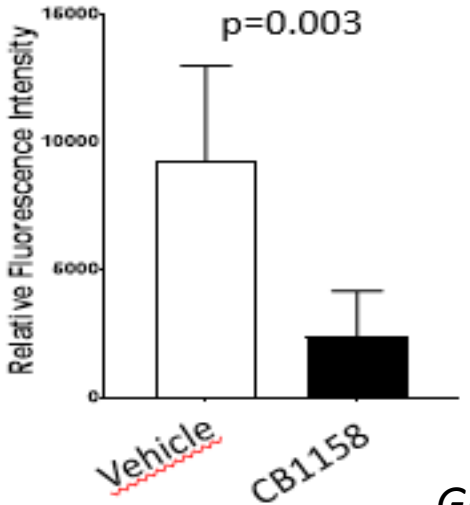
Nor–NOHA
Un inibitore
dell'arginasi



CB1158-Arg1 inhibitor reduces MM engraftment in vivo

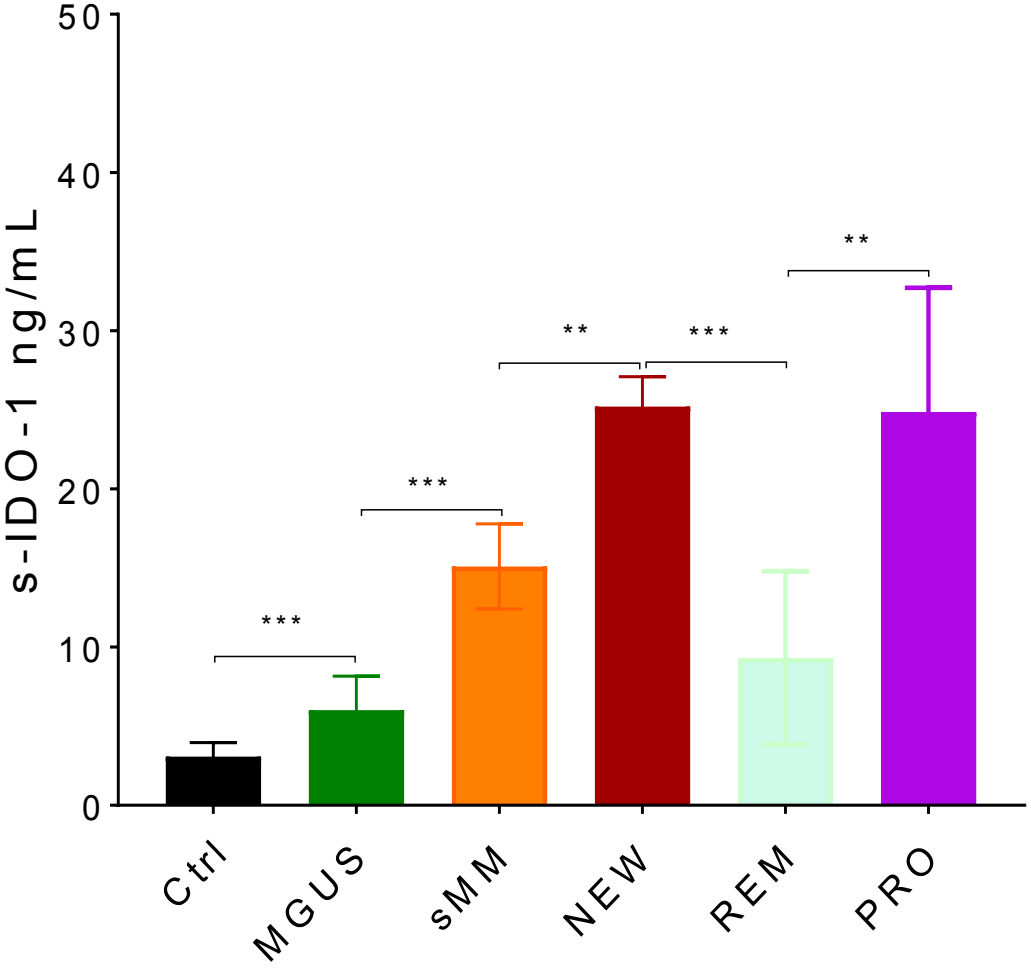


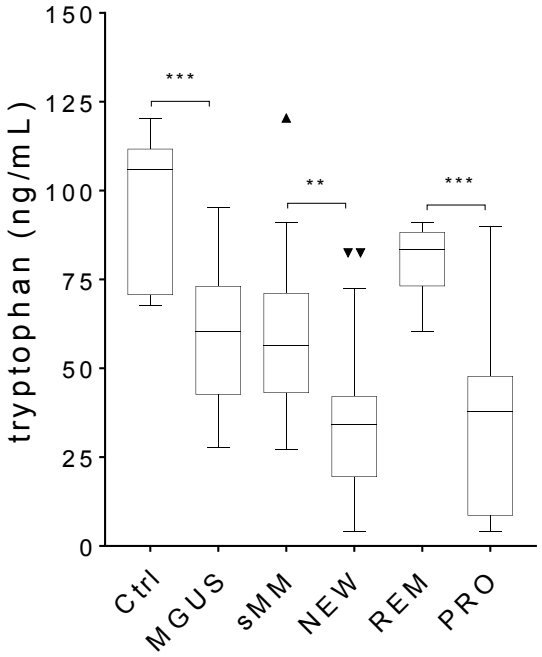


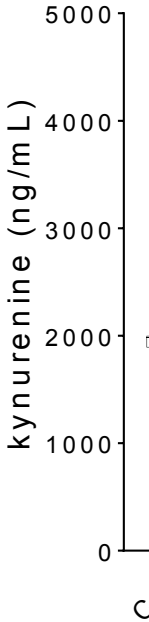


Giallongo and Romano, unpublished data

tryp/KYN is reduced in MM progression due to increased s-IDO-1

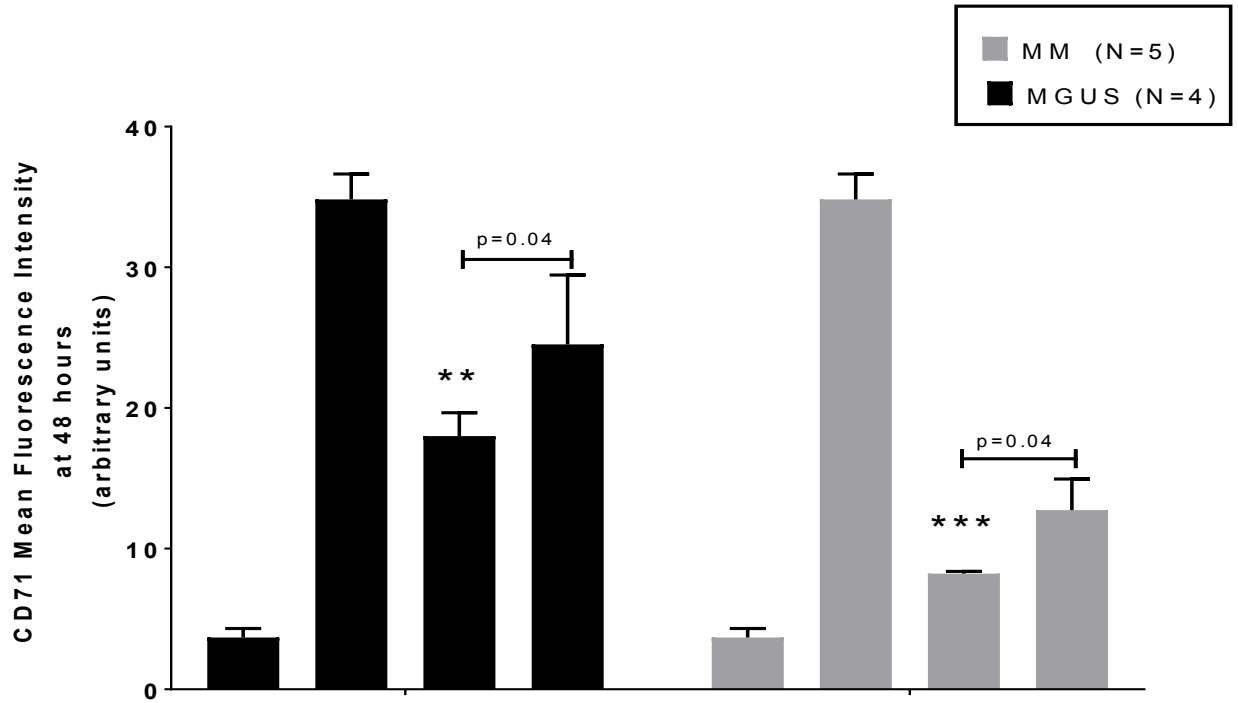






Romano and La Cava, unpublished data

IDO-1 inhibition partially reverts T-cell dysfunction due to HDN



Lymphocyte	+	+	+	+	+	+	+	+
L+PHA	-	+	+	+	-	+	+	+
L+PHA+HDN	-	-	+	+	-	-	+	+
L+PHA+HDN+ INHIBITOR	-	-	-	+	-	-	-	+

Giallongo and Romano, unpublished data

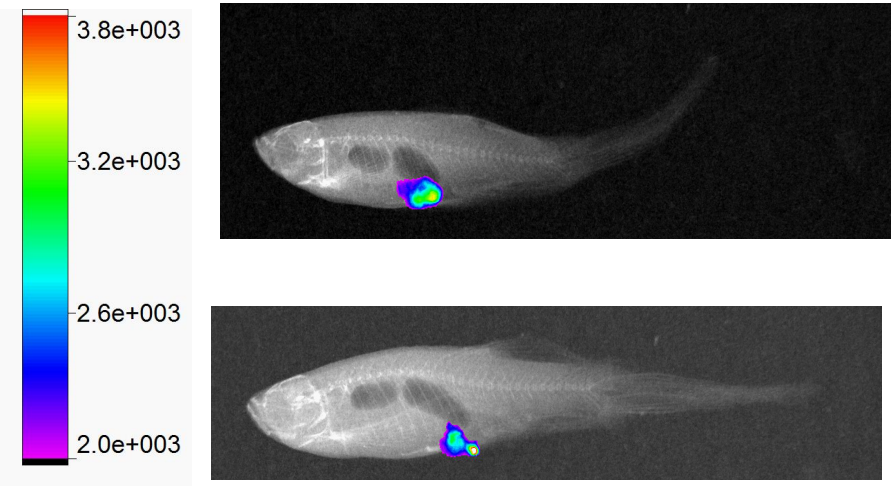
Epacadostat-IDO1 inhibitor has a minor activity in reducing MM engraftment in vivo

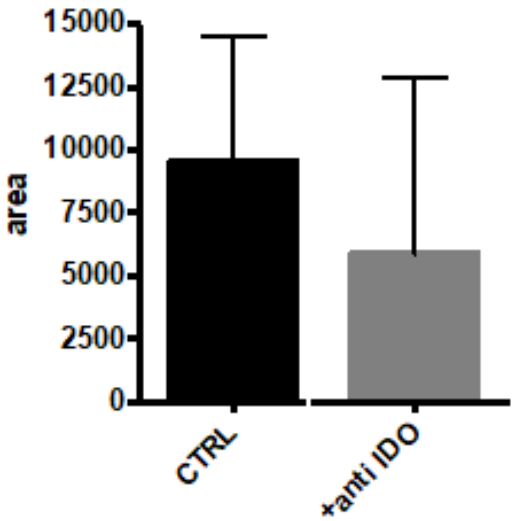
PC injection -/+ inhibitor

+3 d

+ vehicle or + inhibitor

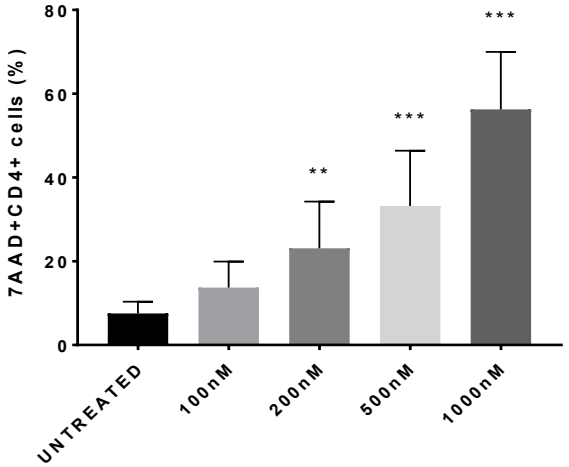
+7 d

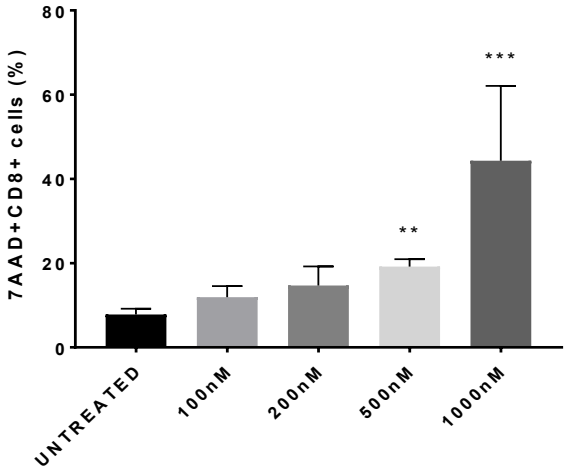


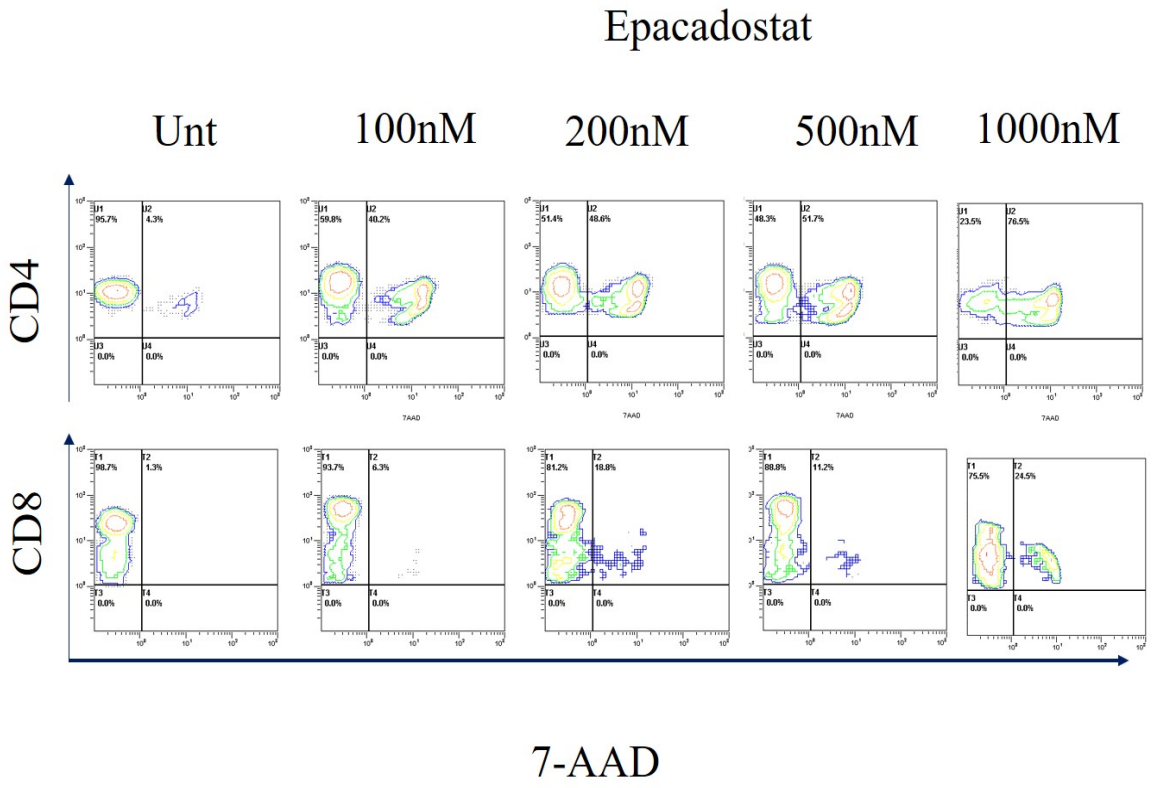


Giallongo and Romano, unpublished data

Increased epacadostat concentration is toxic for T-cells

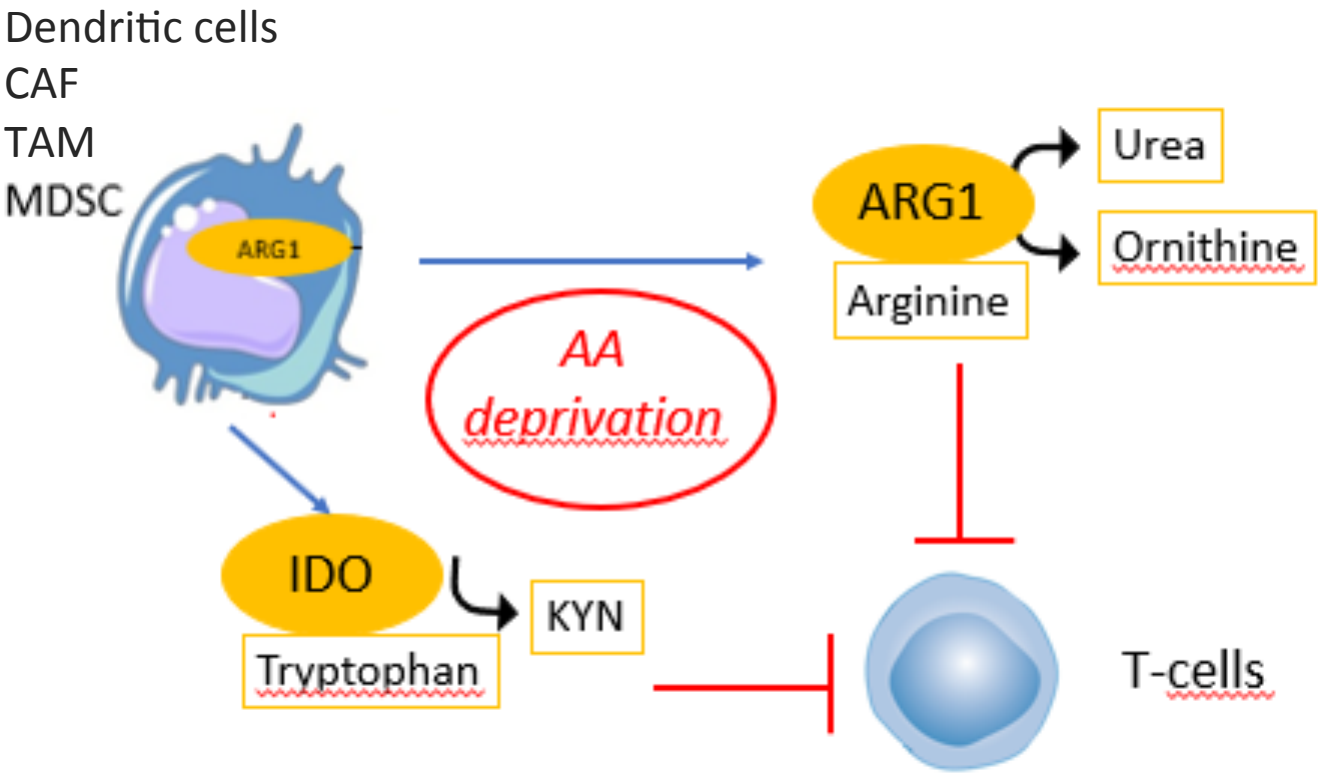




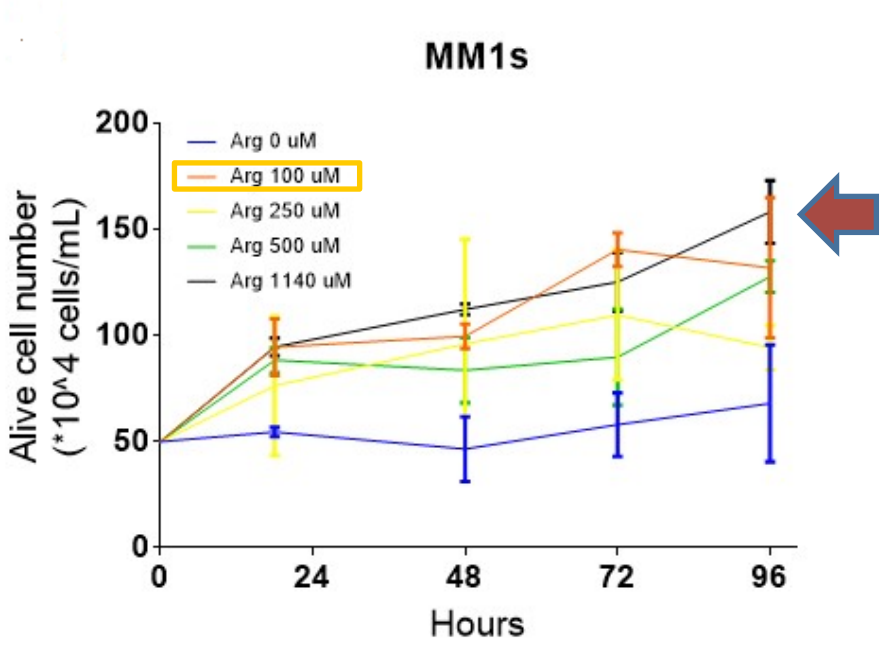


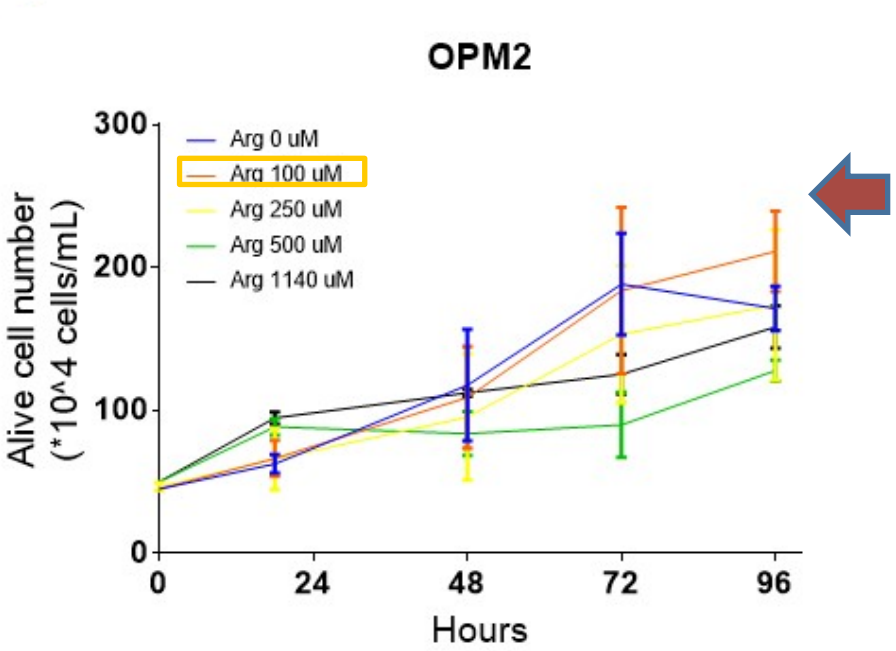
Romano, La Cava, Parrinello unpublished data

Aminoacid degrading enzymes are increased in MM environment



Progressive arginine and tryptophan deprivation do not affect cell viability and proliferation in MM

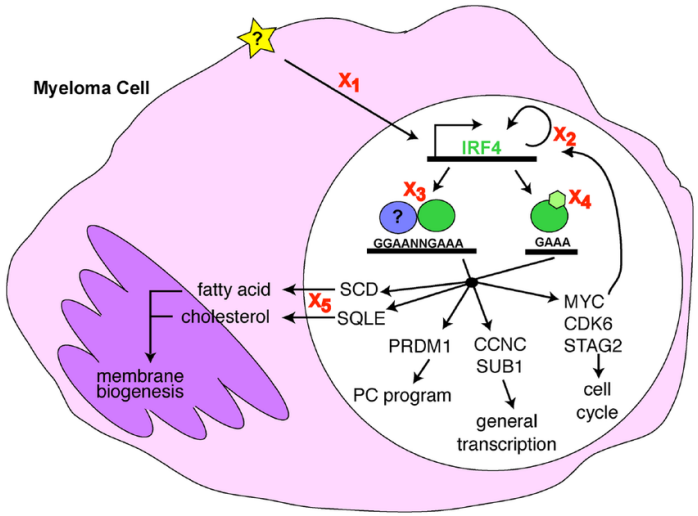




Romano e Cenci

non-oncogene addiction in MM

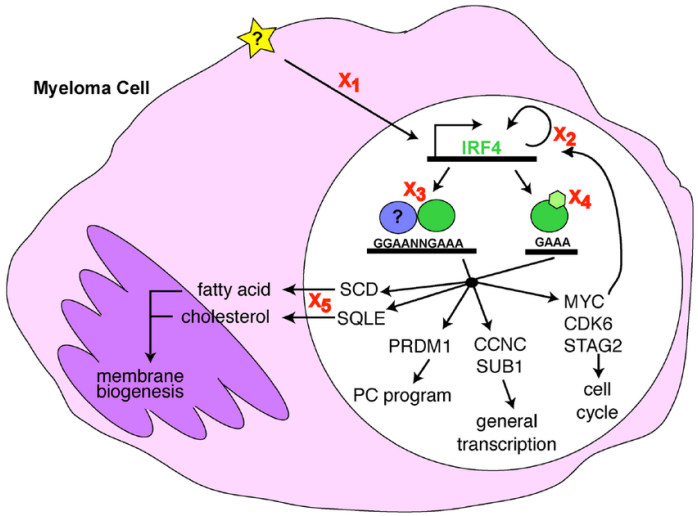
IRF-4



Shaffer,
Nature, 2008

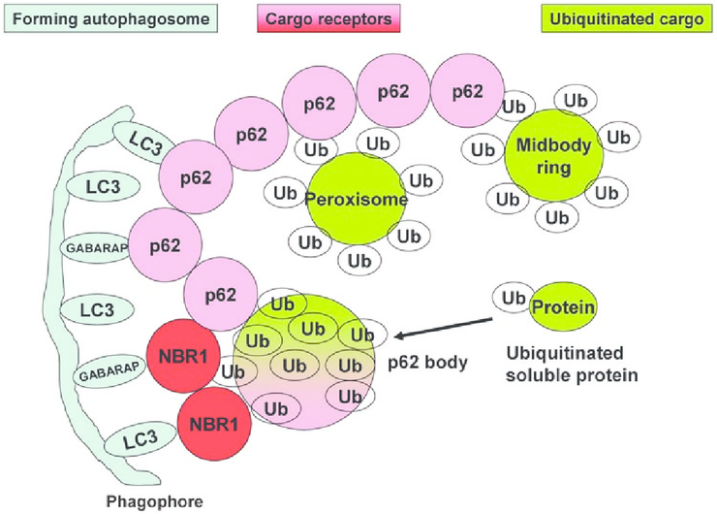
non-oncogene addiction in MM

IRF-4



Shaffer,
Nature, 2008

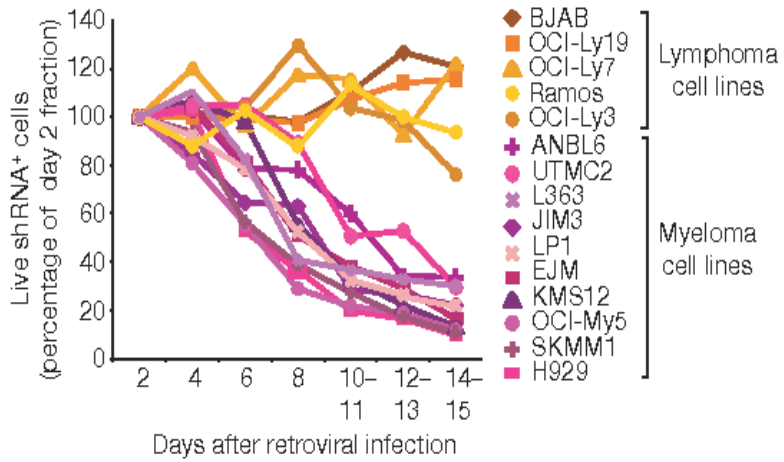
p62



Milan,
Autophagy, 2015

non-oncogene addiction in MM

IRF-4



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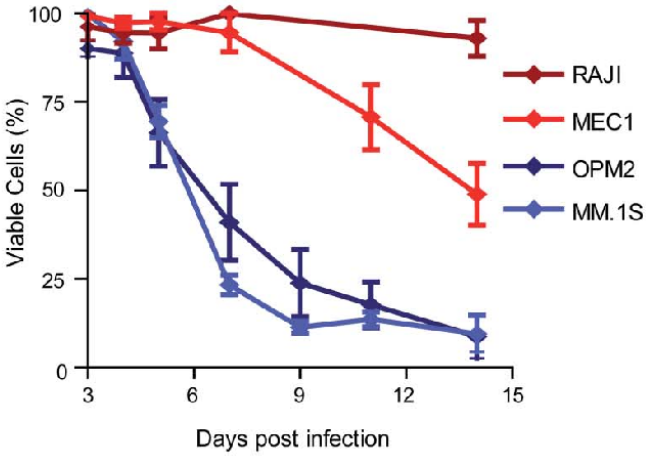
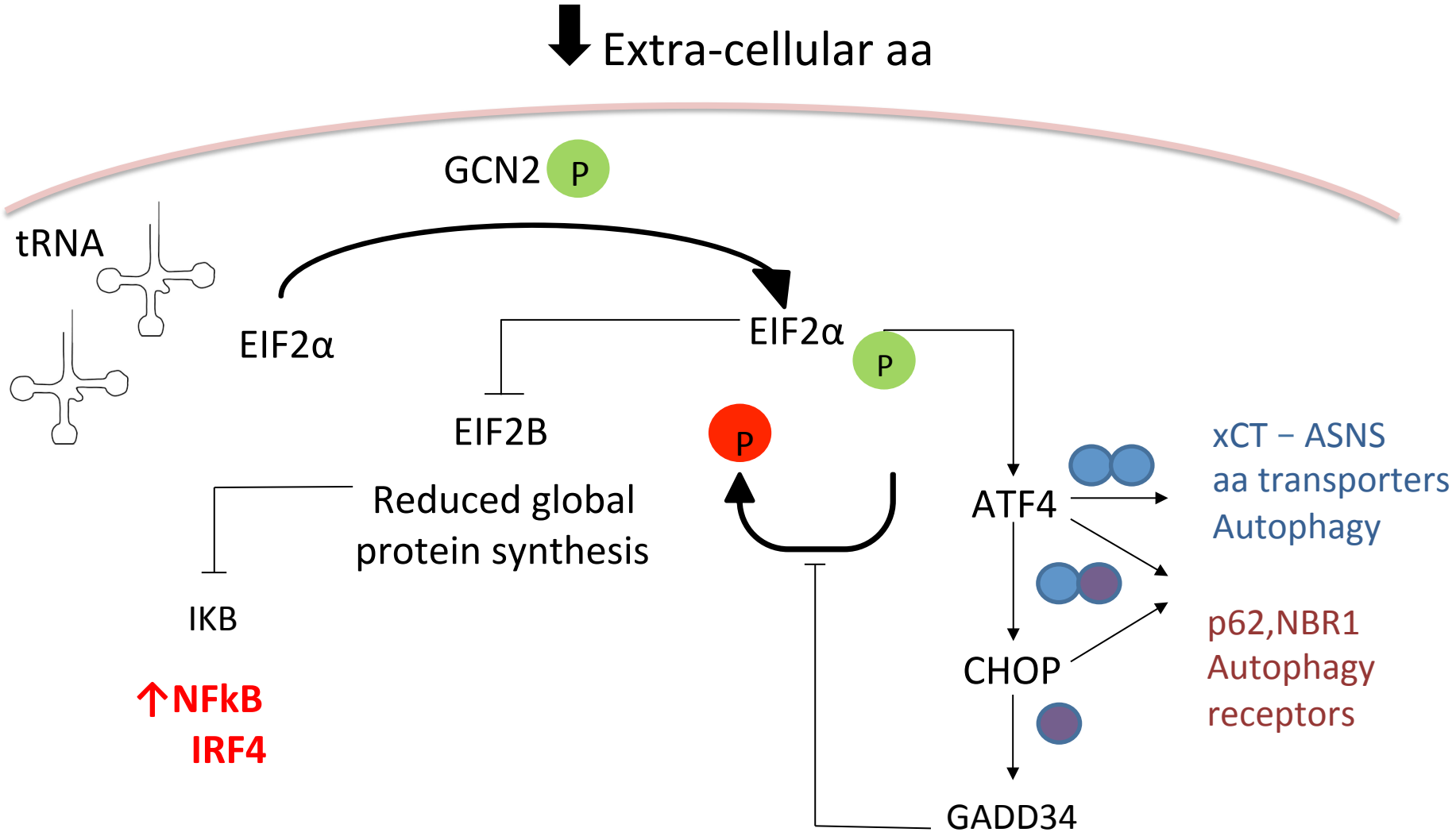


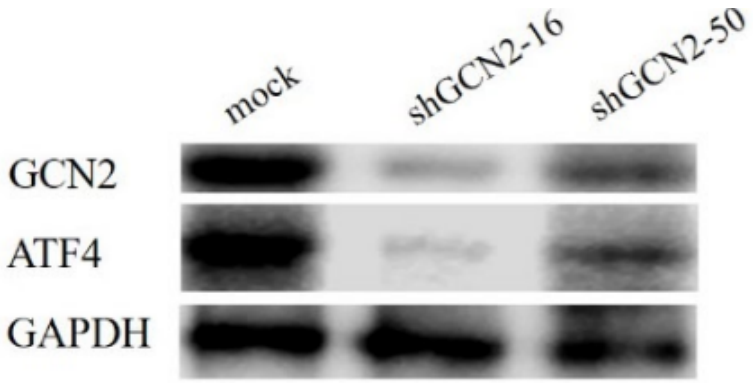
Milan,
Autophagy, 2015

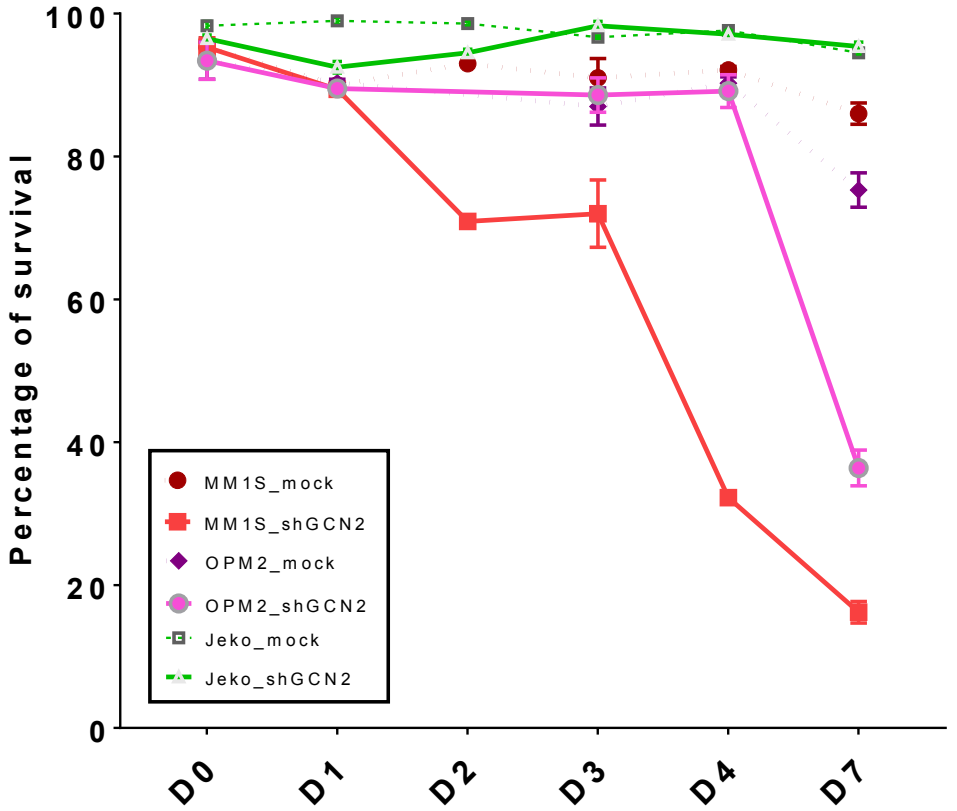
aa deprivation response: GCN2 pathway



B'Chir W., et al. Nucleic acids research. 2013

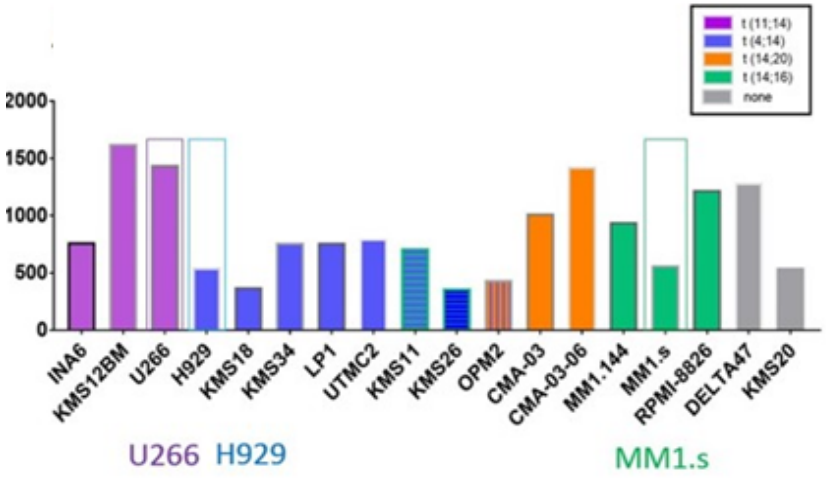
GCN2 is required for MM cells survival

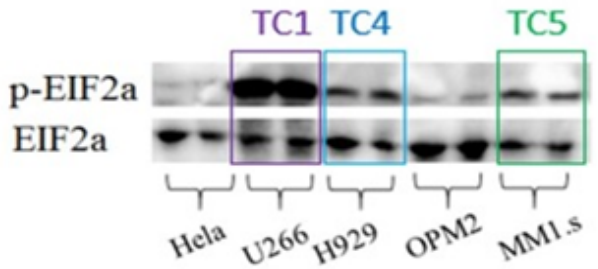


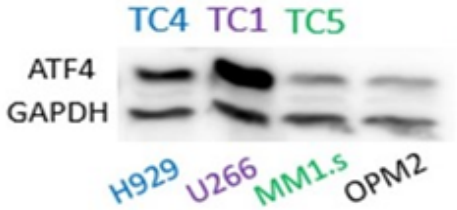


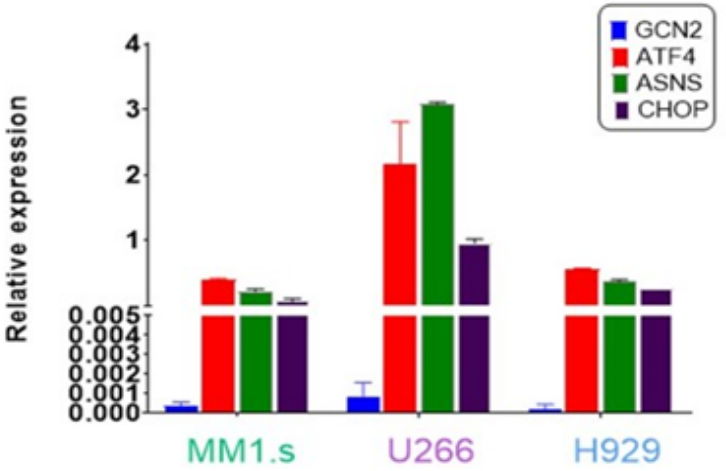
Romano A and Cenci S, unpublished data

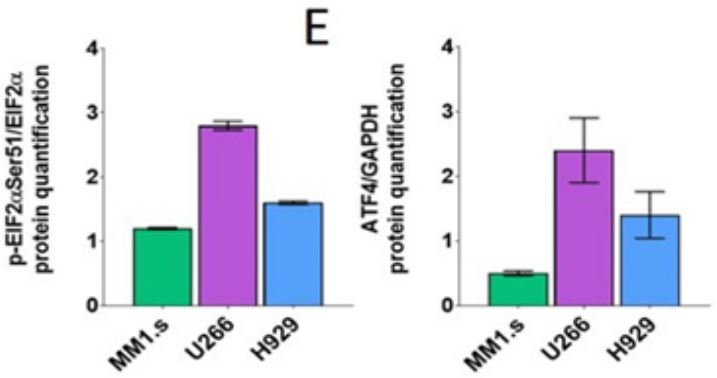
Tonic GCN2 signalling in MM





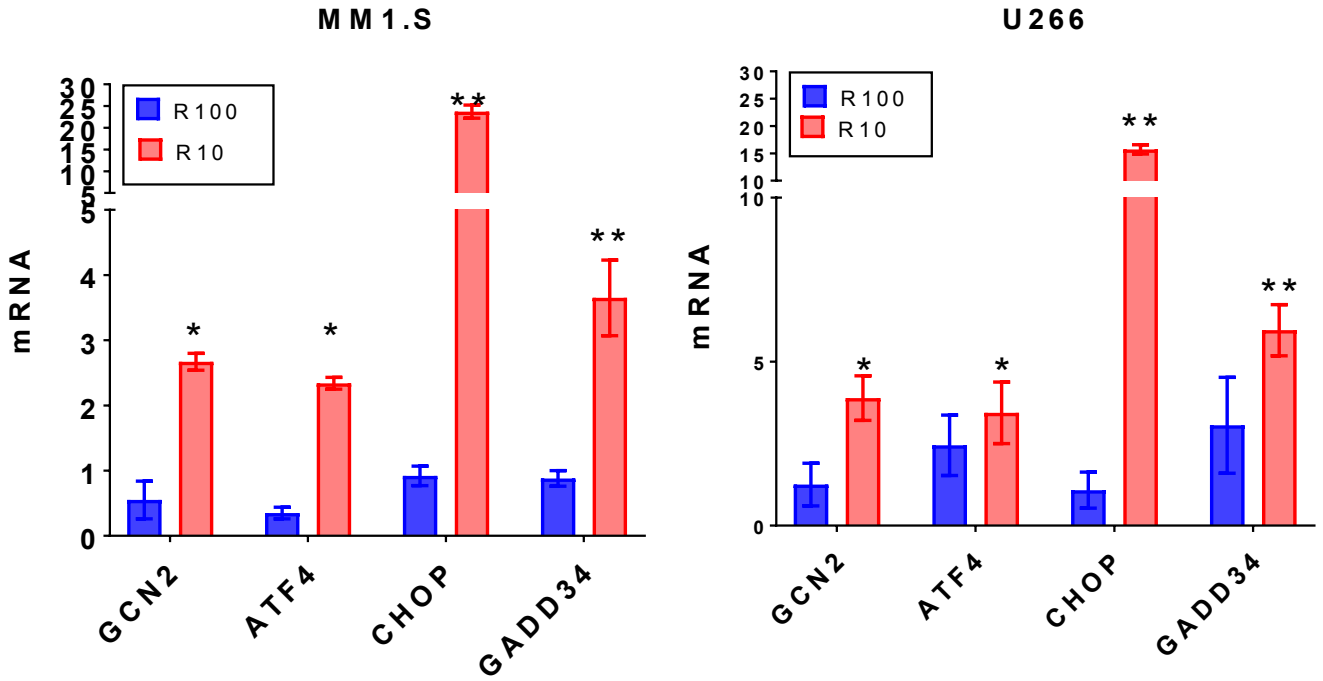






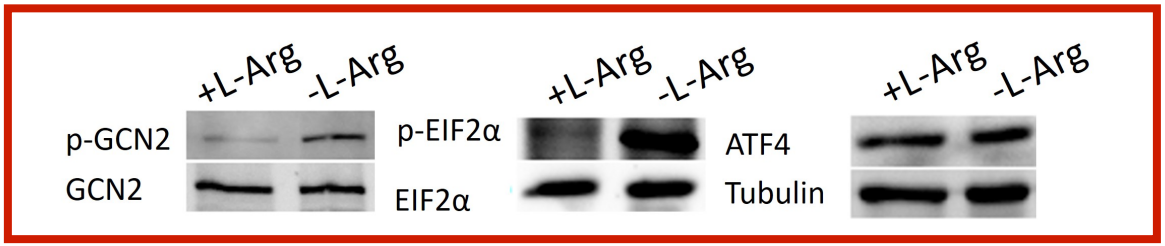
Romano A. and Cenci S. unpublished data

aa deprivation response induces GCN2 in MM



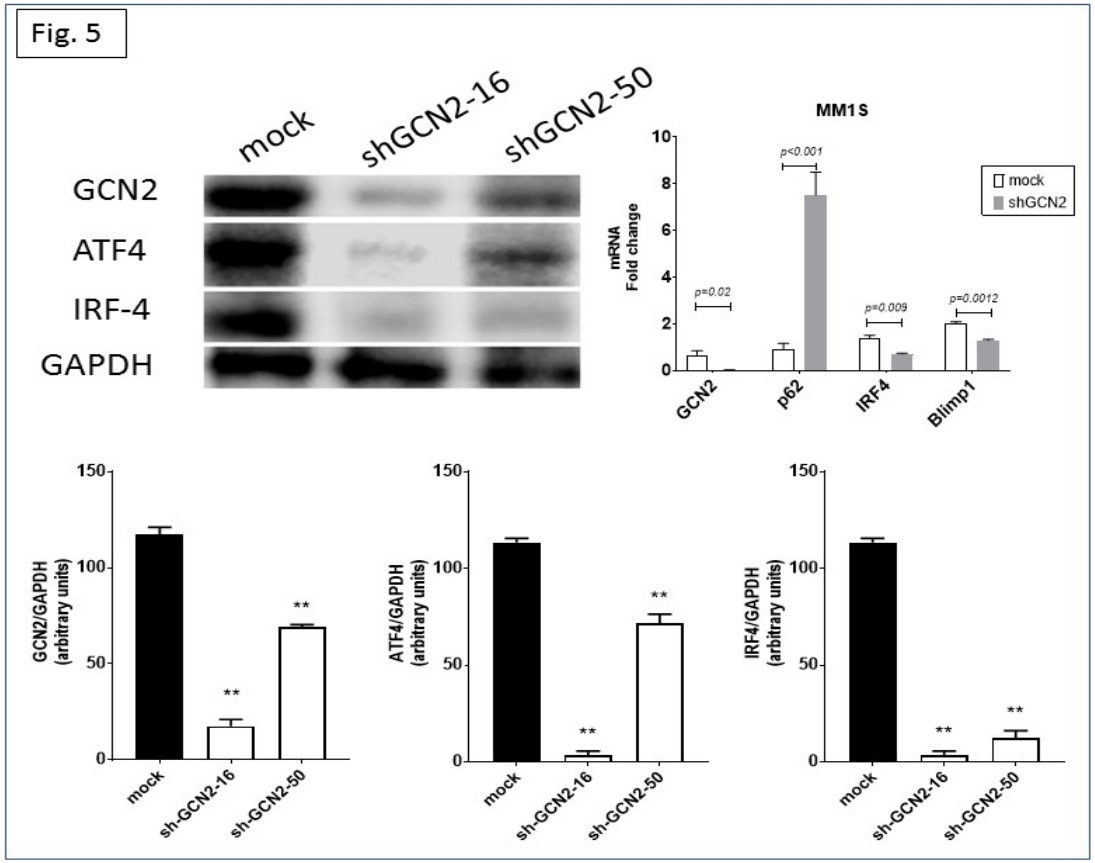
R100: arginine 1140 µM

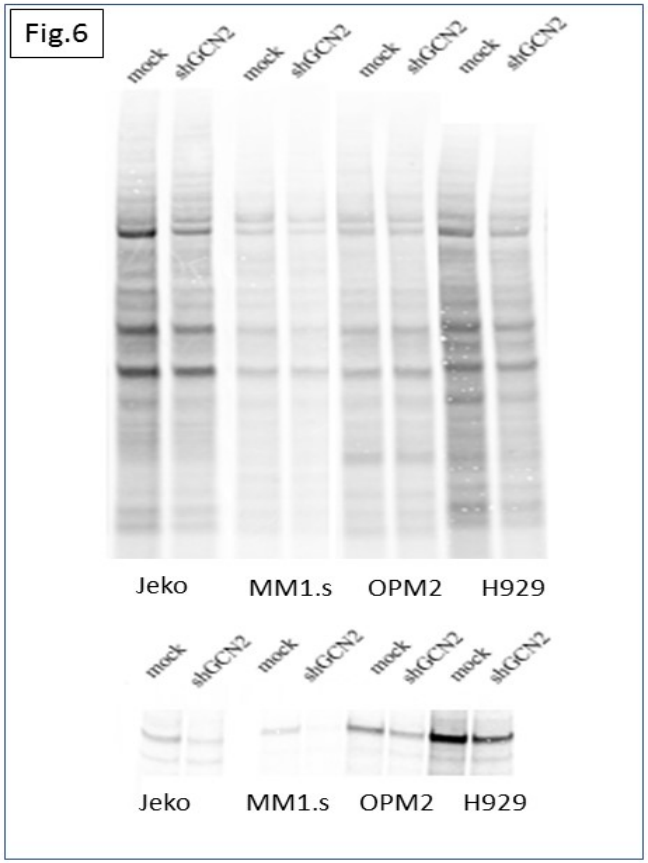
R0: : arginine 0 µM



Romano A. and Cenci S. unpublished data

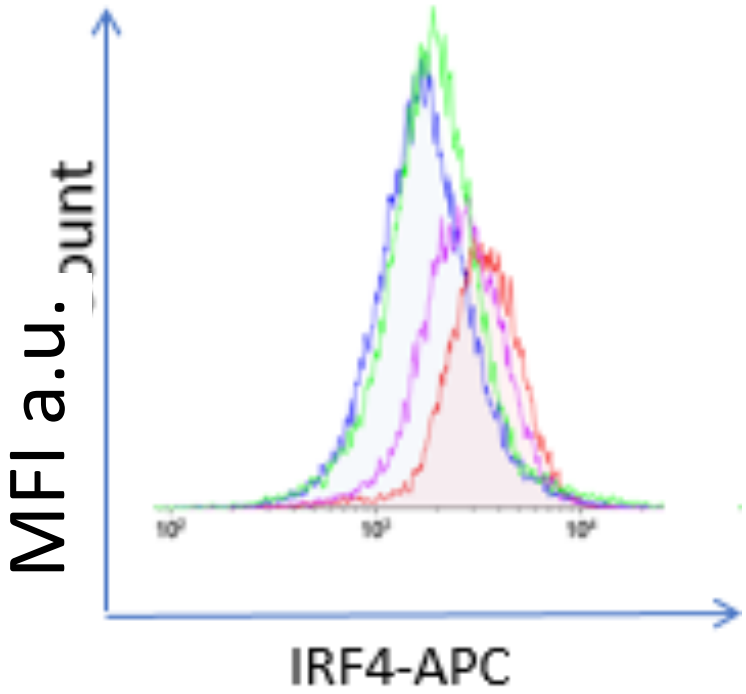
Reduction in GCN2 signalling is associated to IRF4 silencing



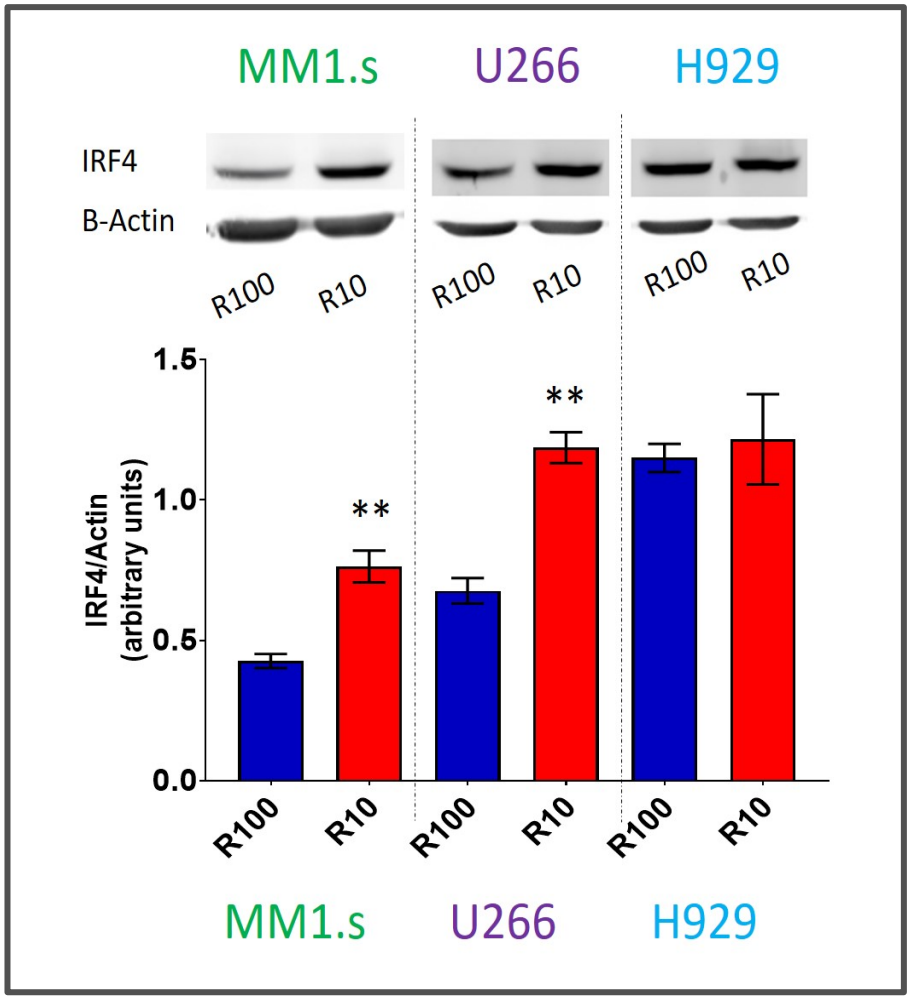


Romano A., Orfanelli U. and Cenci S. unpublished data

Progressive arginine deprivation induces IRF-4

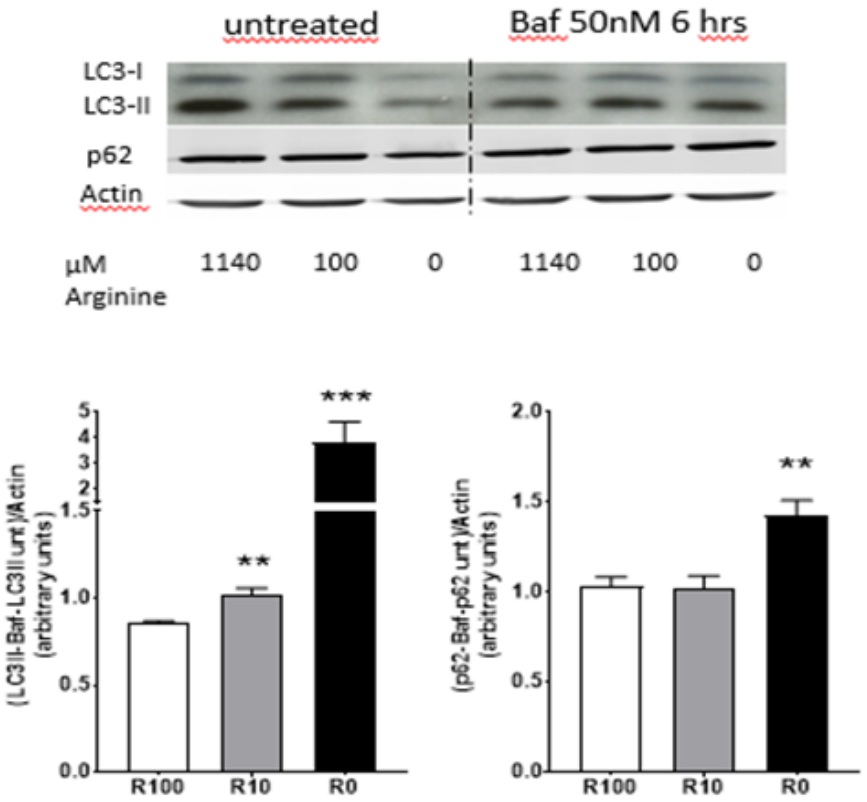


CM: RPMI+FBS, arginine 1140 µM
R100: RPMI+dFBS, arginine 1140 µM
R10: RPMI+dFBS, arginine 100 µM
R0: : RPMI+dFBS, arginine 0 µM



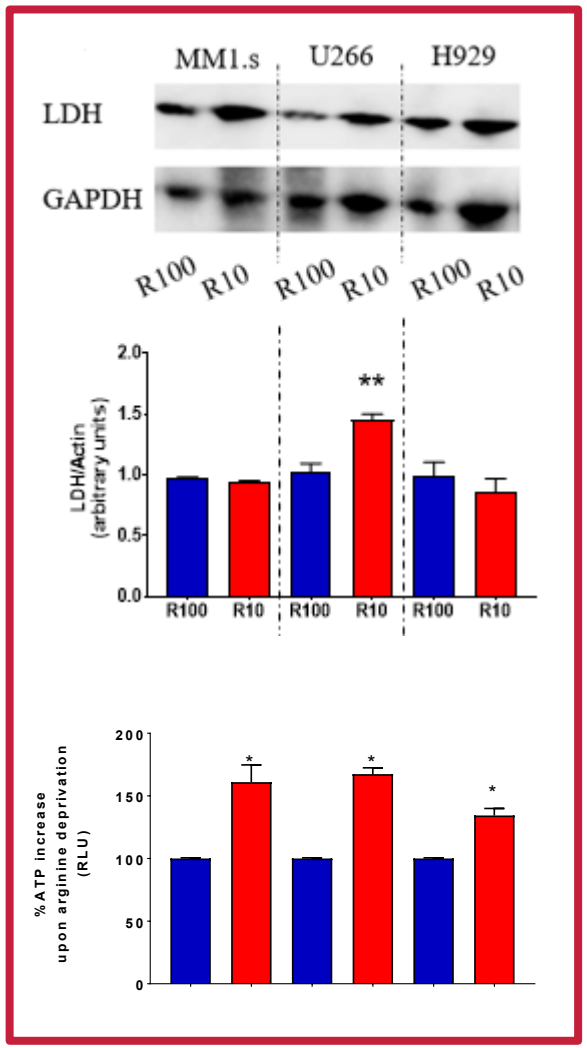
Romano A. and Cenci S. unpublished data

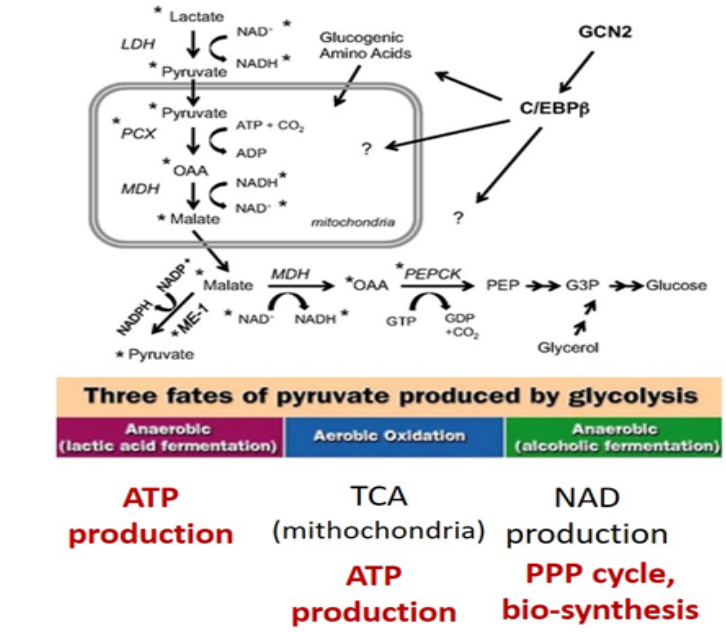
Progressive arginine deprivation induces autophagy flux

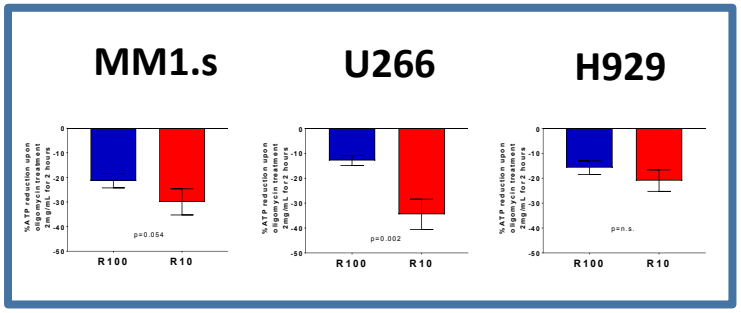


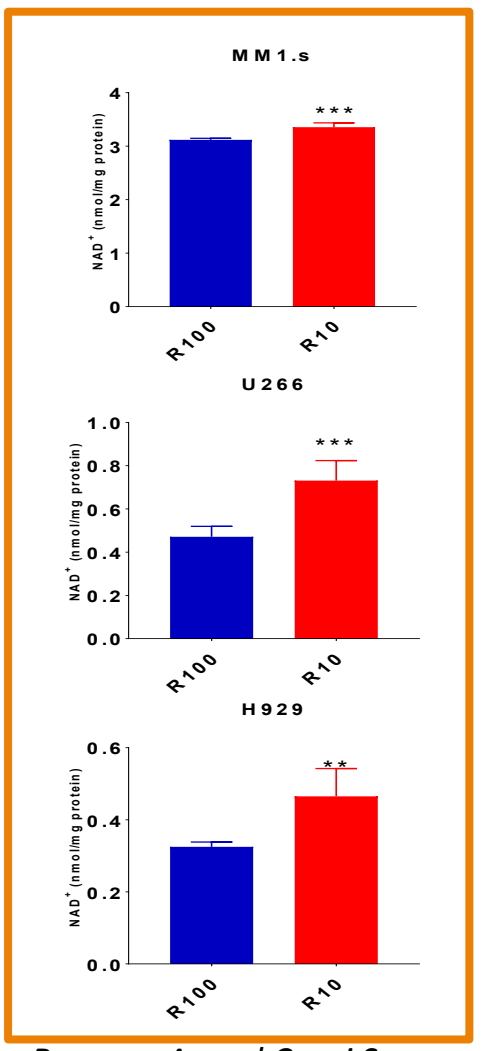
Romano A. and Cenci S.
unpublished data

Bioenergetics of MM cells upon arginine deprivation









Romano A. and Cenci S. unpublished data

MDSC and HDN

conclusions

↑ aminoacids degrading enzymes

MM competence

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IRCCS CROB
Istituto di Ricovero e Cura a Carattere Scientifico

Simone Cenci

OSPEDALE SAN RAFFAELE

Ministero della Salute
DIPARTIMENTO DELLA SANITA' PUBBLICA E DELL'INNOVAZIONE
DIREZIONE GENERALE DELLA RICERCA SANITARIA E BIOMEDICA E DELLA VIGILANZA SUGLI ENTI
RICERCA FINALIZZATA 2011-2012

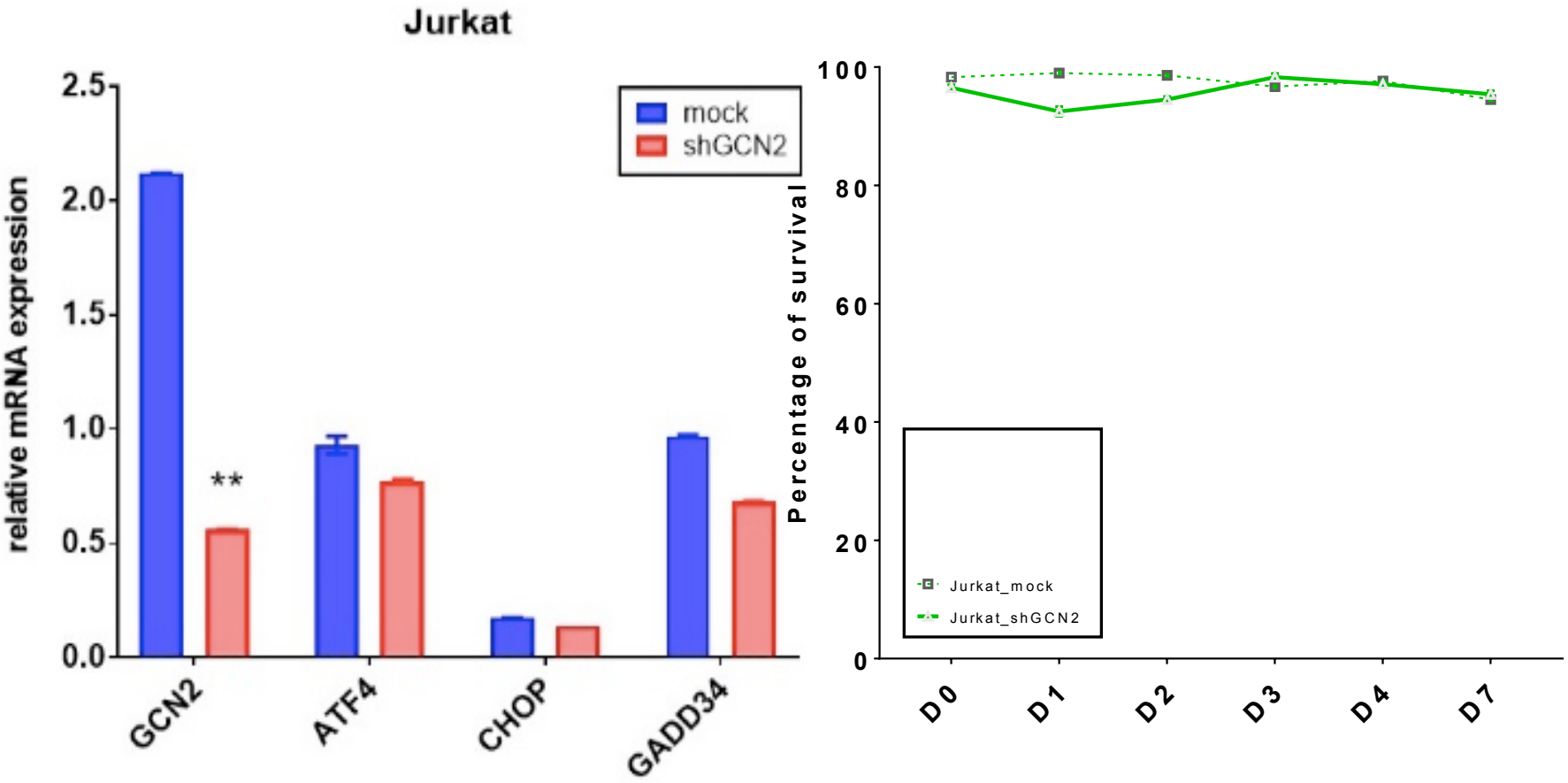
FON.CA.NE.SA. onlus
Anche quest'anno hai una possibilità unica per aiutare la Fon.Ca.Ne.Sa. onlus, destinando il 5xmille dell'IRPEF - P. IVA/C.F. 02299950879

International Myeloma Foundation

AIL

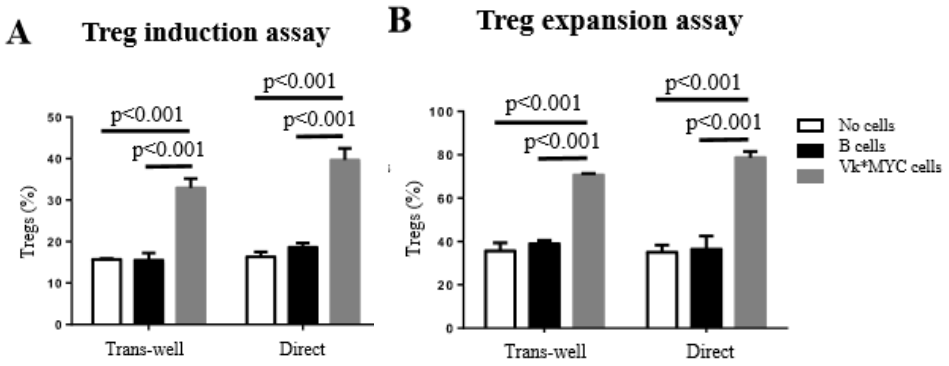
Ιπποκράτης
(HIPPOCRATES)

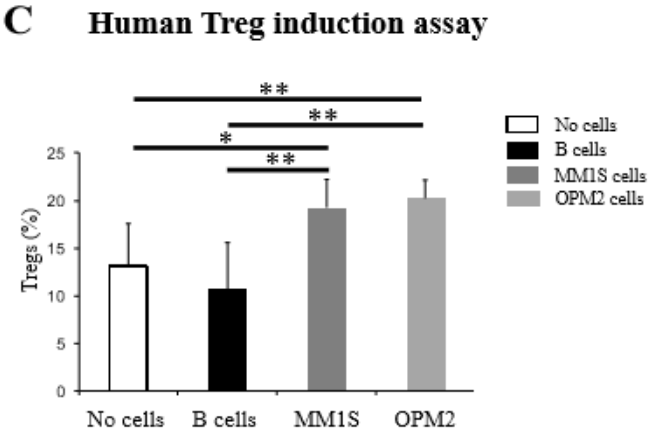
GCN2 is required for MM but not for T-cell lymphoma survival

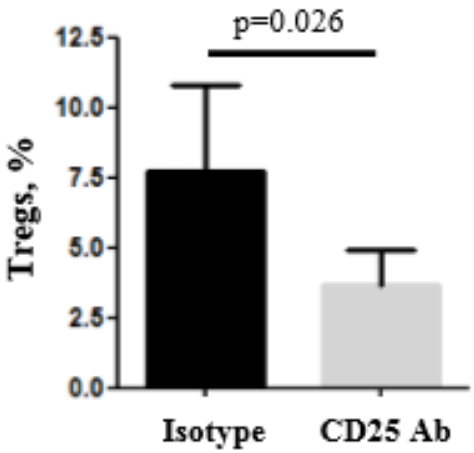


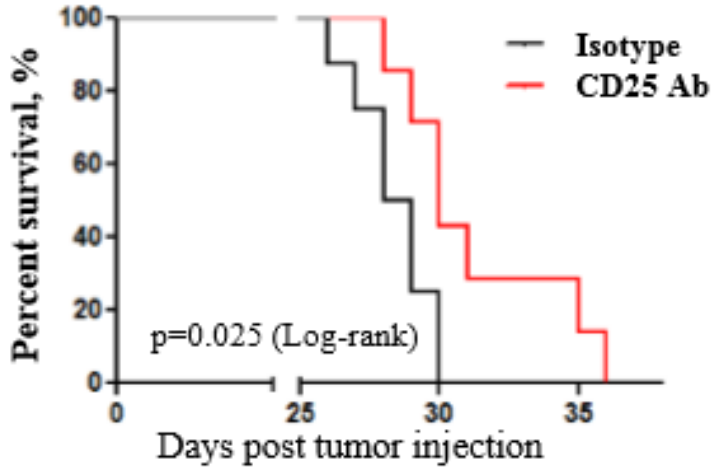
Romano e Cenci

MM cells induce and expand T-regs in vitro and in vivo



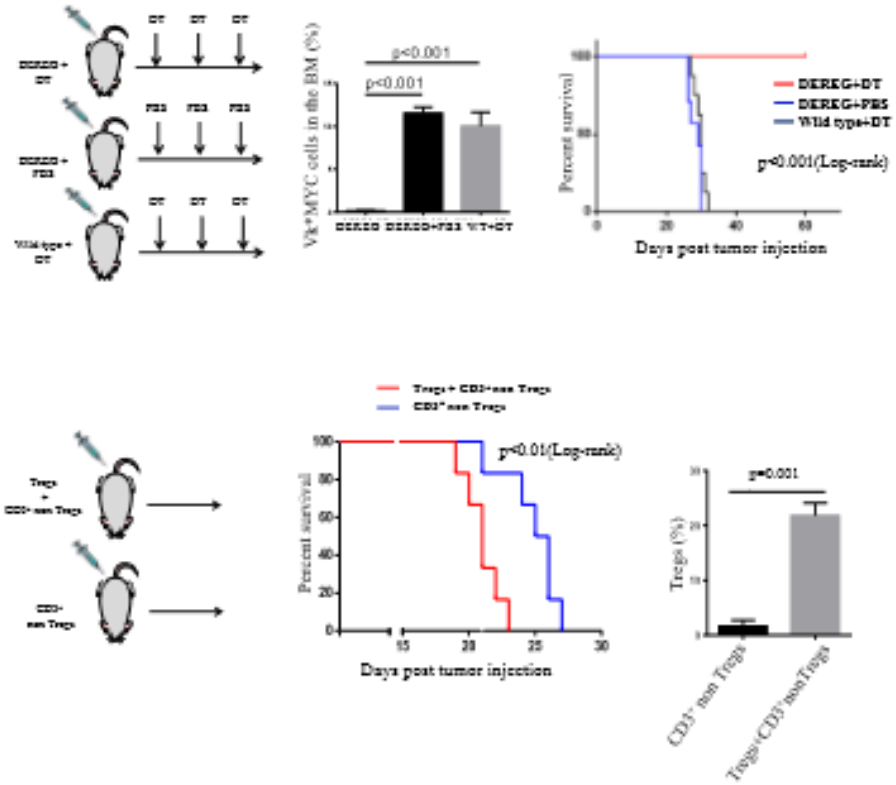




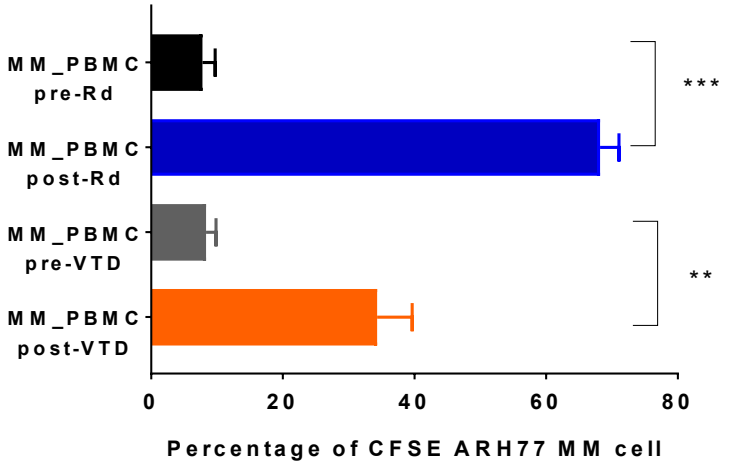


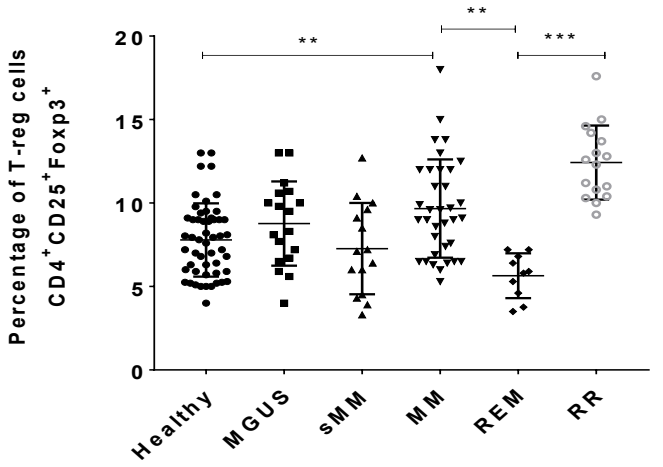
Kawano, JCI 2018

Reduction of T-regs is associated to clinical response



Kawano, JCI 2018





Parrinello, unpublished data