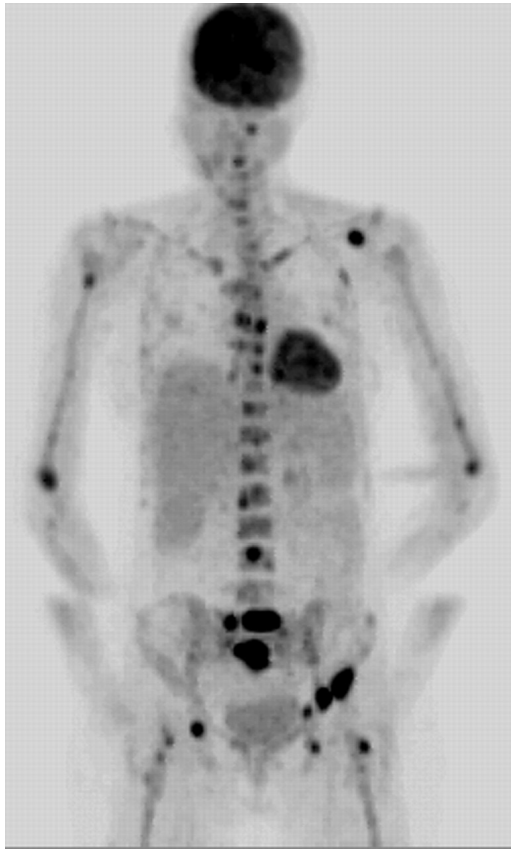
EMERGING THERAPEUTIC TARGETS IN MULTIPLE MYELOMA

Michele Cea, MD

Clinic of Hematology
Department of Internal Medicine (DiMI), University of Genoa
IRCCS Policlinic Hospital San Martino
Genoa, Italy

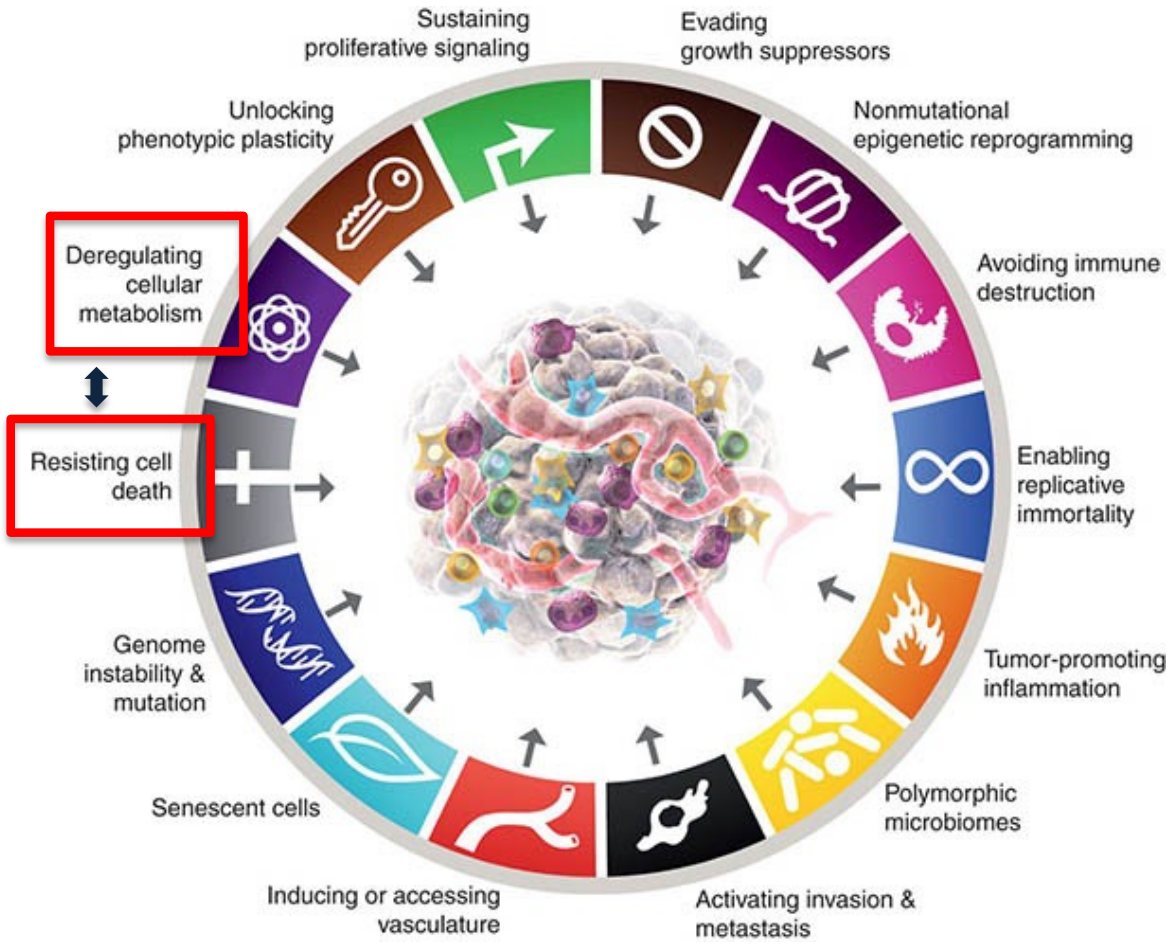
2023 Multiple Myeloma Updates: from bench to bedside
Genoa, Italy 20-21 November 2023

DEREGULATING METABOLISM IS A CANCER HALLMARK



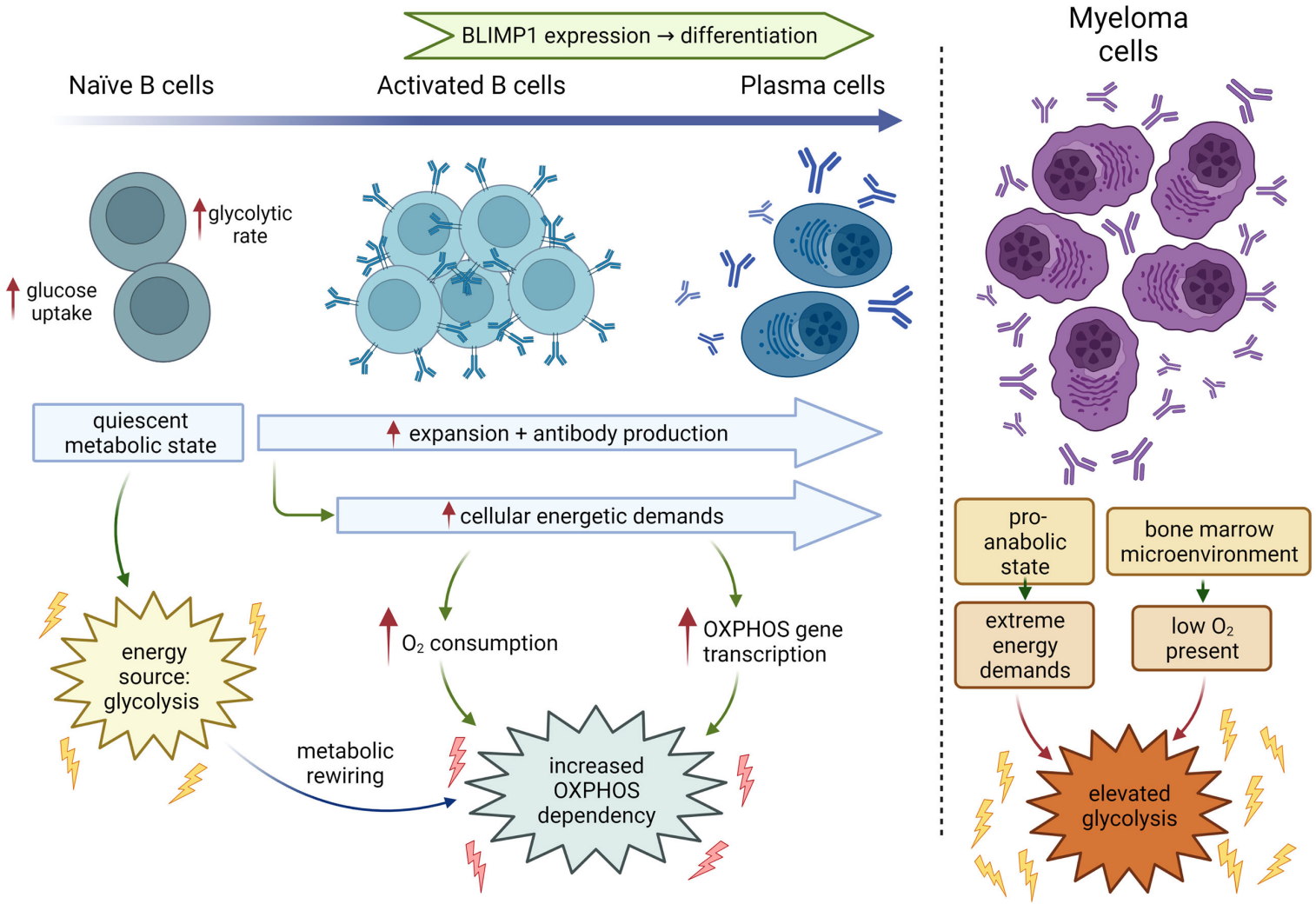
[10^{F}] Fluorodeoxyglucose-PET scan

Bredella MA. et al. AJR Am J Roentgenol 2005 Apr;184(4):1199-204



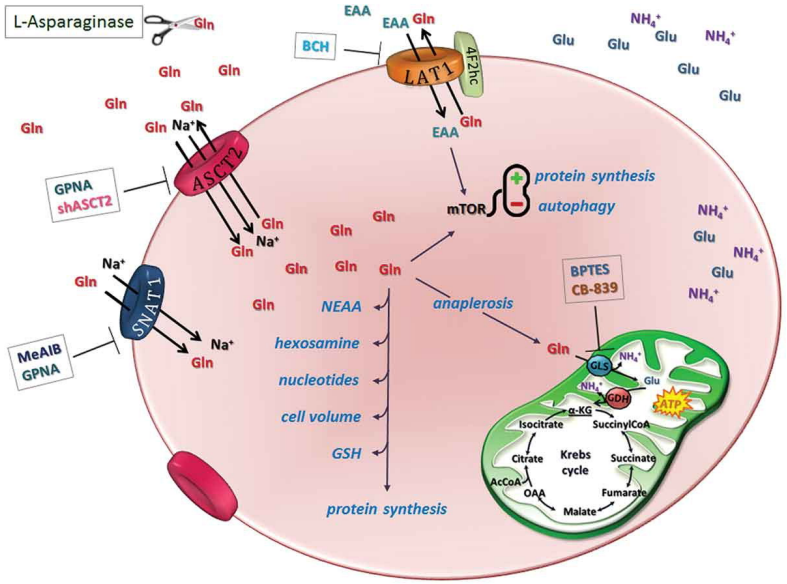
Hanahan D. et al. Cancer Discovery 2022 12 (1): 31-46

METABOLIC CHANGES DURING B-CELL DIFFERENTIATION

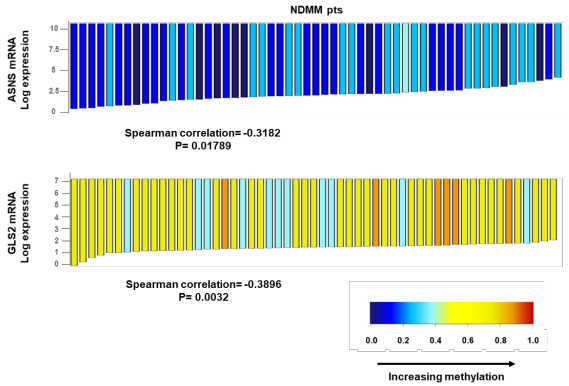


Nair R. et al. Front Oncol 2022 Sep 16:12:1000106

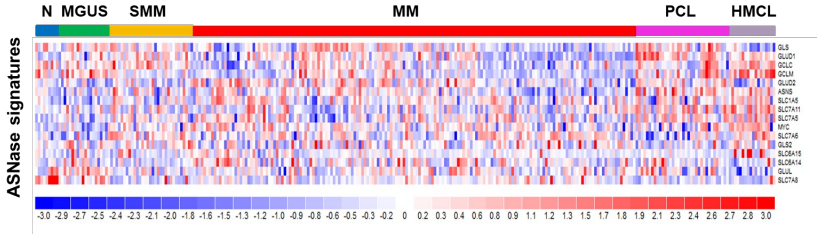
AMINO ACID DEPLETION AS THERAPEUTIC TARGETS FOR MULTIPLE MYELOMA

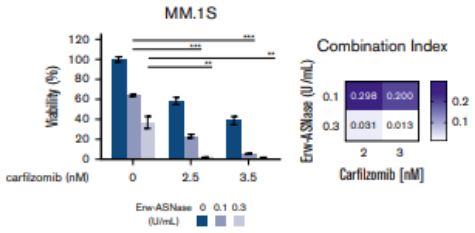


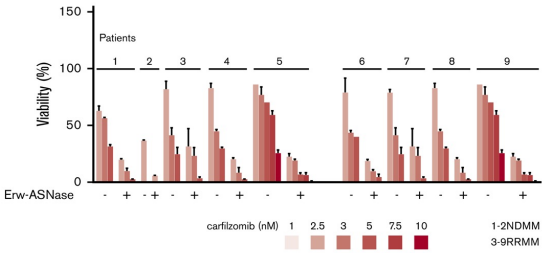
Giuliani N. et al. Expert Opin Ther Targets 2017 Mar;21(3):231-234



Debora Soncini, PhD

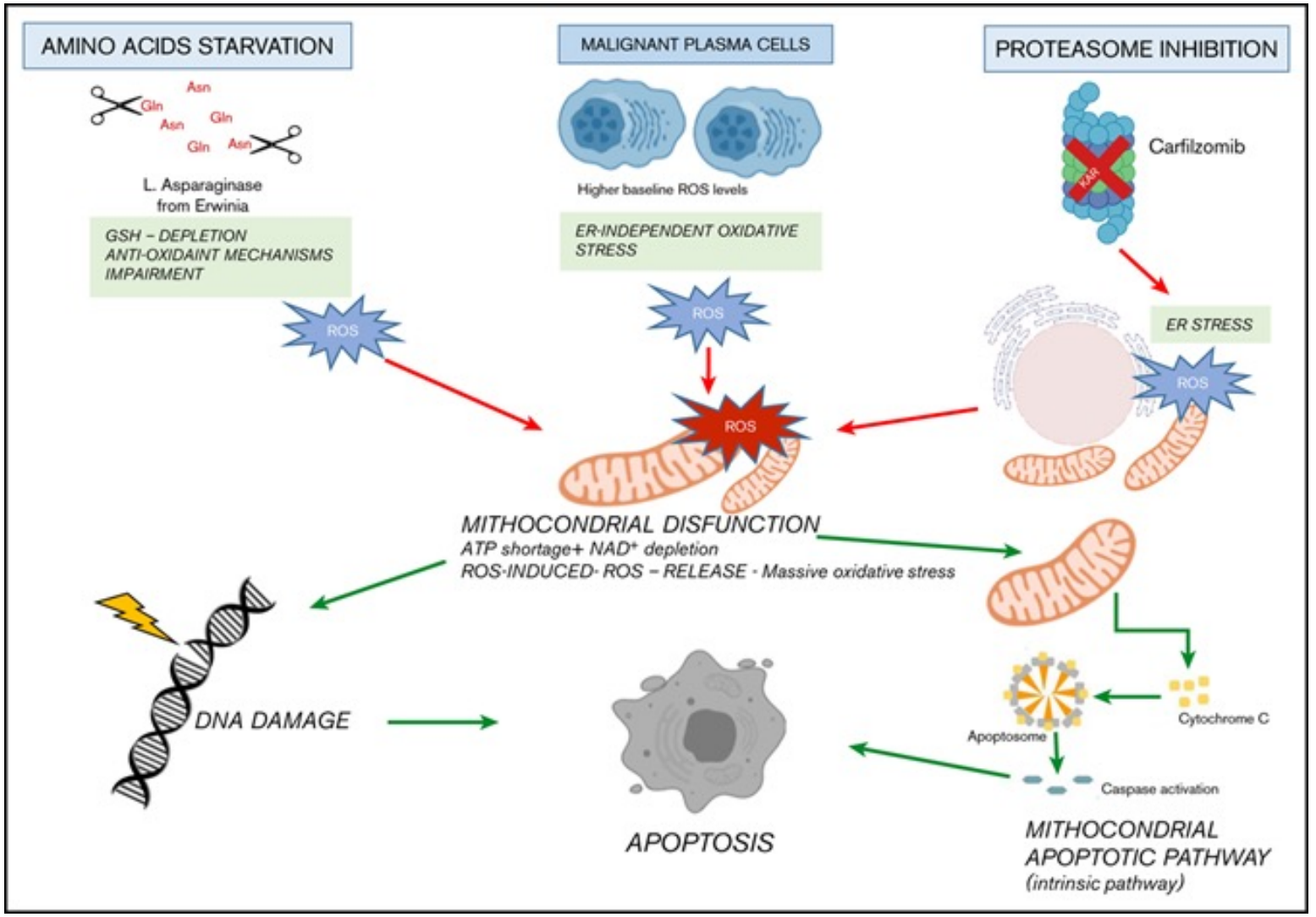






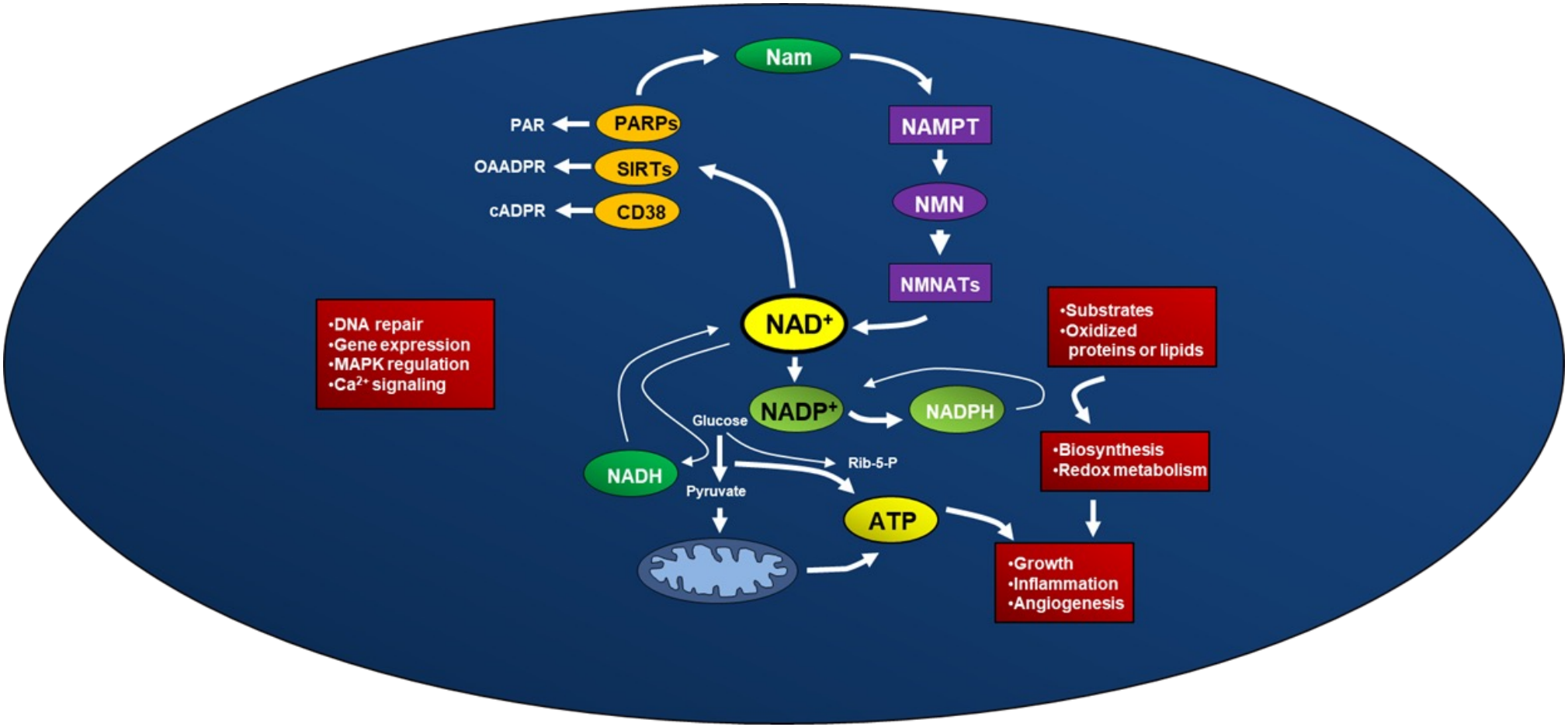
Soncini et al. Blood Adv, 2020 Sep 22;4(18):4312-4326,

AMINO ACID DEPLETION TRIGGERED BY L-ASPARAGINASE SENSITIZES MM CELLS TO CARFILZOMIB BY INDUCING MITOCHONDRIA ROS-MEDIATED CELL DEATH



Soncini et al. Blood Adv, 2020 Sep 22;4(18):4312-4326,

TARGETING NAD+ METABOLISM IN MULTIPLE MYELOMA



Cea M. et al. Blood. 2009 Jun 4;113(23):6035-7
Cea M. et al. Blood. 2012 Oct 25;120(17):3519-29
Cagnetta A. et al. Blood 2013 Aug 15;122(7):1243-55
Cea M. et al. Autophagy 2013 Mar:9(3):410-2
Soncini D. et al. J Biol Chem 2014 Dec 5;289(49):34189-24

Cagnetta A. et al. Clin. Cancer Res. 2015 Sep 1;21(17):3934-45
Cea M. et al. Clin. Cancer Res. 2016 Dec 15;22(24):6099-6109
Cea M. et al. Blood. 2016 Mar 3;127(9):1138-50
Biniecka P. et al. Molecules. 2023 Feb 16;28(4):1897
Becherini P. et al. Antioxidants (Basel) 2023 Feb 15;12(2):494

MYELOMA EXIBITH ALTERED NAD + METABOLISM: THERAPEUTIC IMPLICATIONS

LYMPHOID NEOPLASIA

Targeting NAD$^+$ salvage pathway induces autophagy in multiple myeloma cells via mTORC1 and extracellular signal-regulated kinase (ERK1/2) inhibition

*Michele Cea,[1,2] *Antonia Cagnetta,[1,3] Mariateresa Fulciniti,[1] Yu-Tzu Tai,[1] Teru Hideshima,[1] Dharminder Chauhan,[1] Aldo Roccaro,[1] Antonio Sacco,[1] Teresa Calimeri,[1] Francesca Cottini,[1] Jana Jakubikova,[1] Sun-Young Kong,[1,4] Franco Patrone,[2] Alessio Nencioni,[2] Marco Gobbi,[3] Paul Richardson,[1] Nikhil Munshi,[1] and Kenneth C. Anderson[1]

[1]LeBow Institute for Myeloma Therapeutics and Jerome Lipper Center for Multiple Myeloma Research, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Departments of [2]Internal Medicine and [3]Hematology and Oncology, Istituto Di Ricovero e Cura a Carattere Scientifico Azienda Ospedaliera Universitaria San Martino-IST, Genova, Italy; and [4]Research Institute and Hospital, National Cancer Center, Goyang, Korea

Blood. 2012 Oct 25;120(17):3519-29.

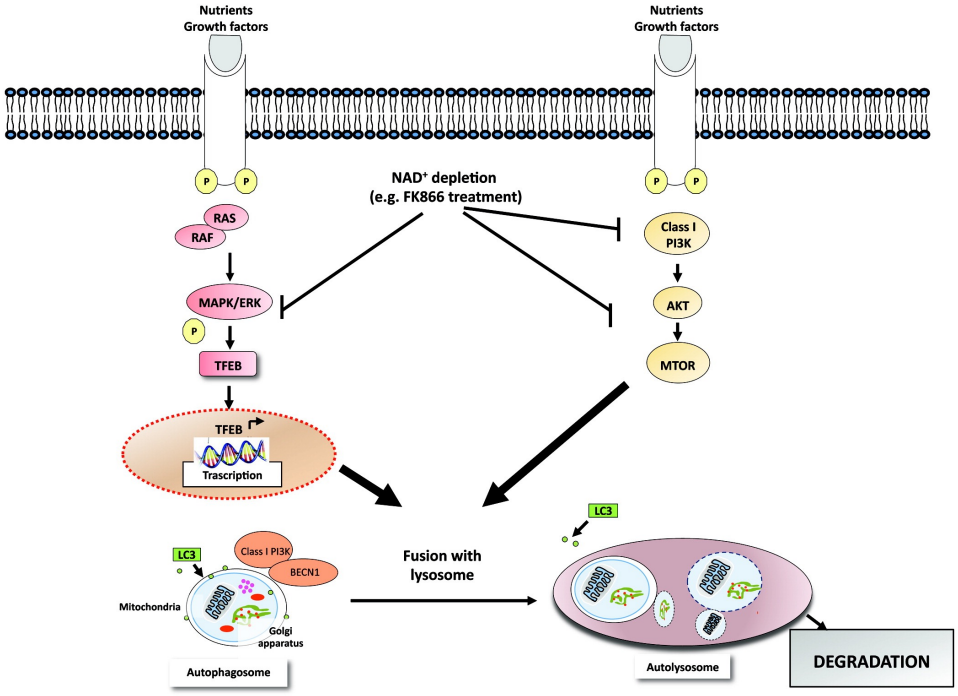
LYMPHOID NEOPLASIA

Intracellular NAD$^+$ depletion enhances bortezomib-induced anti-myeloma activity

Antonia Cagnetta,[1,2] Michele Cea,[1,2] Teresa Calimeri,[1] Chirag Acharya,[1] Mariateresa Fulciniti,[1] Yu-Tzu Tai,[1] Teru Hideshima,[1] Dharminder Chauhan,[1] Mike Y. Zhong,[1] Franco Patrone,[3] Alessio Nencioni,[3] Marco Gobbi,[2] Paul Richardson,[1] Nikhil Munshi,[1] and Kenneth C. Anderson[1]

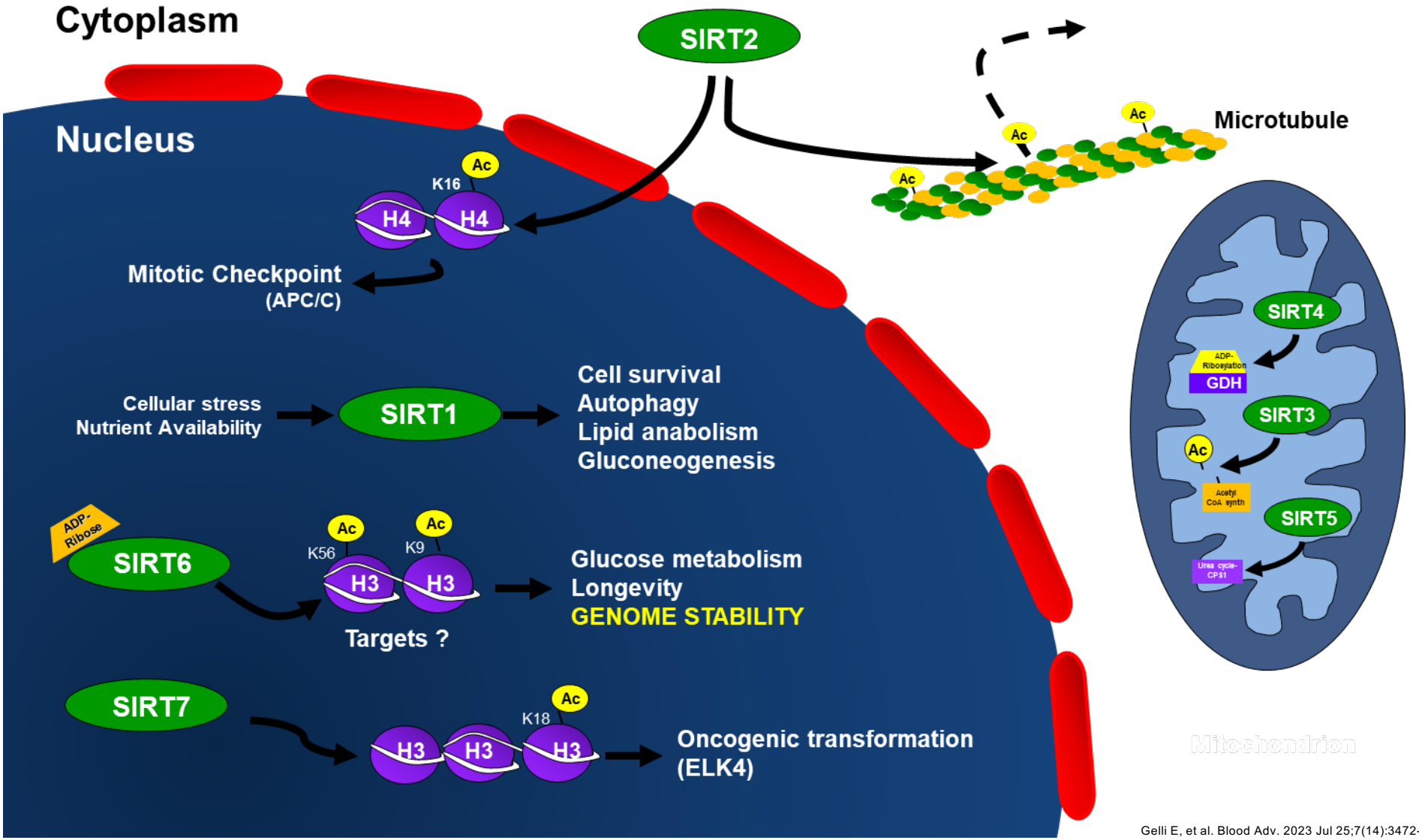
[1]LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; and [2]Department of Hematology and Oncology, and [3]Departments of Internal Medicine, Istituto Di Ricovero e Cura a Carattere Scientifico Azienda Ospedaliera Universitaria San Martino-IST, Genova, Italy

Blood 2013 Aug 15;122(7):1243-55



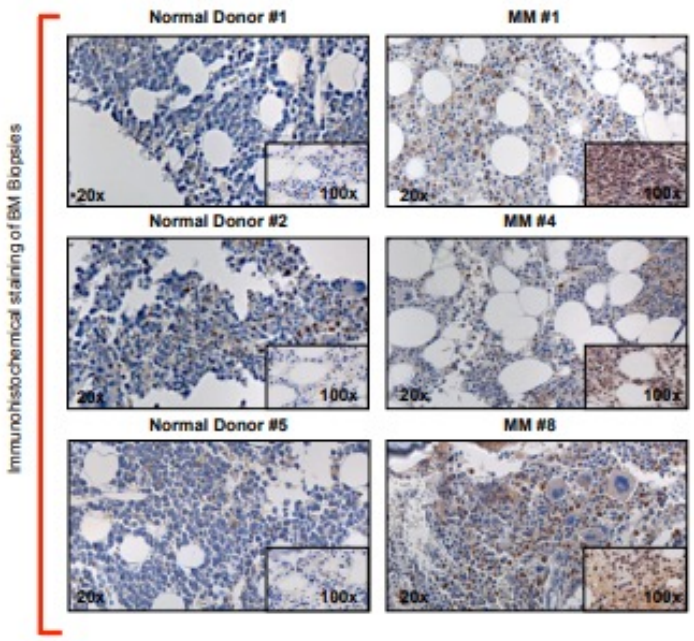
…….Overall we found an increased sensitivity of MM cells to NAD$^+$-lowering agents

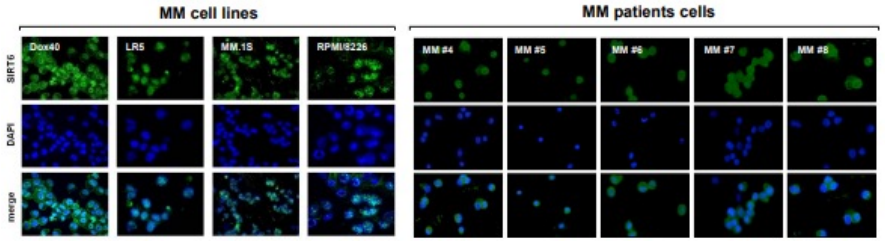
TARGETING NAD+ USERS IN MULTIPLE MYELOMA: SIRTs (part I)

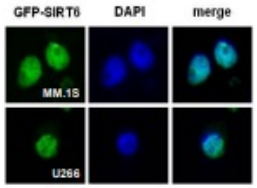


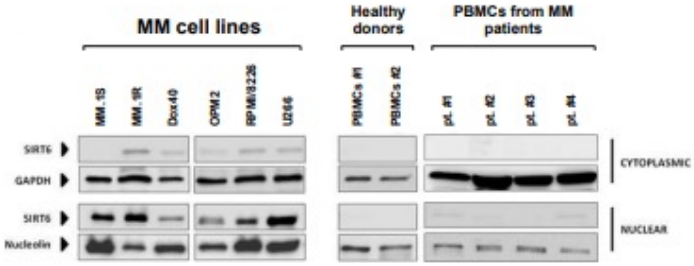
Gelli E, et al. Blood Adv. 2023 Jul 25;7(14):3472-3478
Becherini P, et al.Cancer Metab. 2021 Jan 22;9(1):6
Cagnetta A, et al.Haematologica. 2018 Jan;103(1):80-90
Cea M, et al.Blood. 2016 Mar 3;127(9):1138-50
Bauer I, et al. J Biol Chem. 2012 Nov 30;287(49):40924-37
Cea M, et al. A.PLoS One. 2011;6(7):e22739

EVIDENCE FOR A ROLE OF THE HISTONE DEACETYLASE SIRT6 IN DNA DAMAGE RESPONSE OF MULTIPLE MYELOMA CELLS

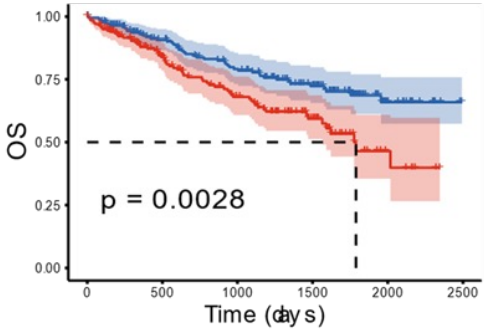


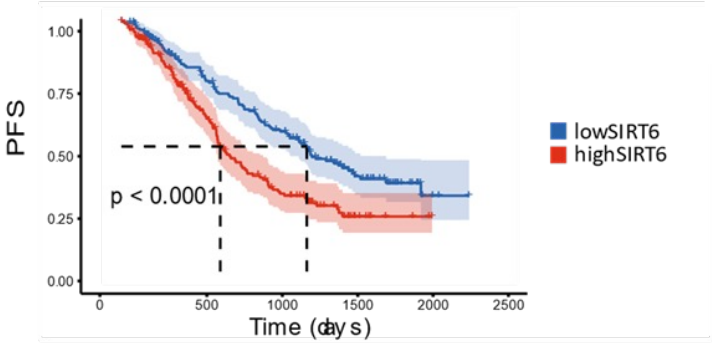


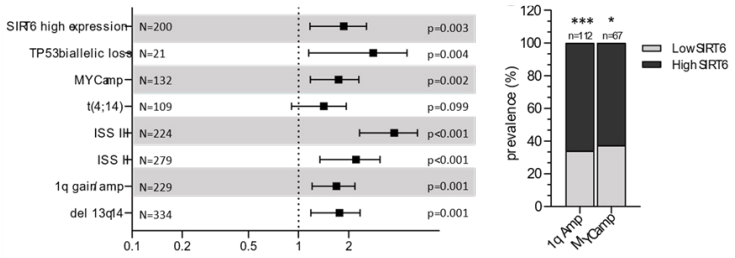




Cea M. et al. Blood 2016 Mar 3;127(9):1138-50,







Gelli E, et al. Blood Adv. 2023 Jul 25;7(14):3472-3478

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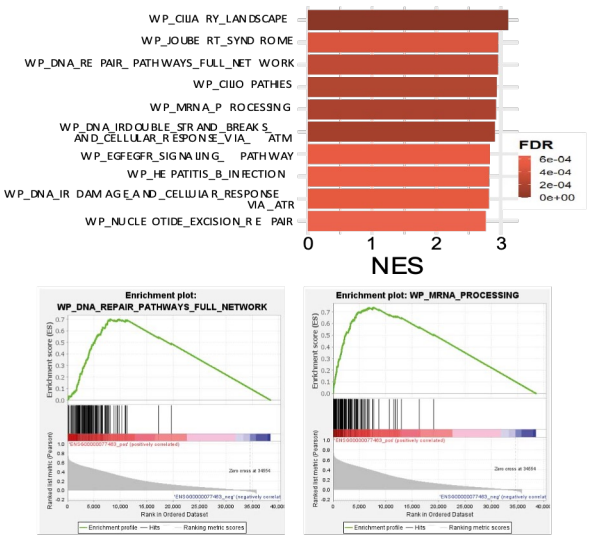

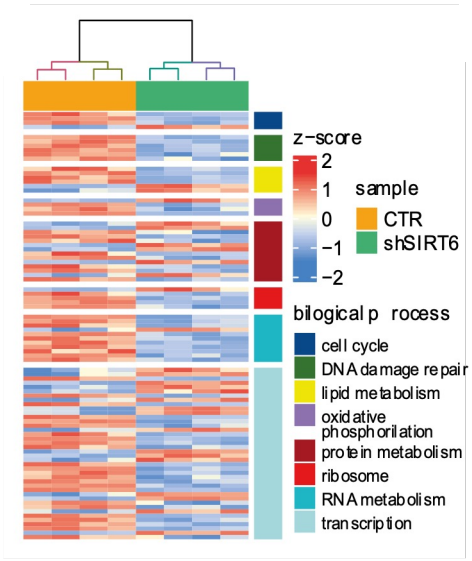

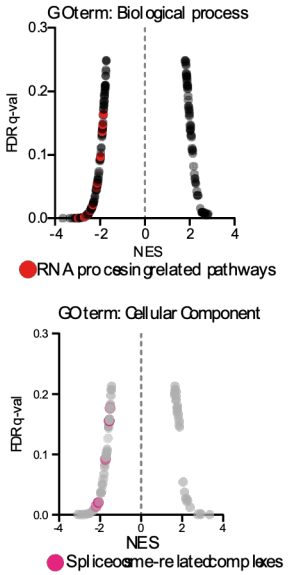

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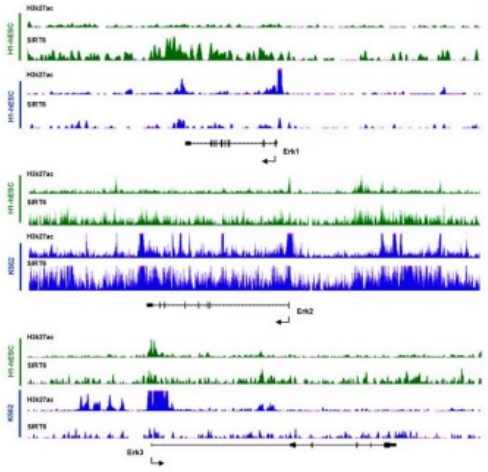

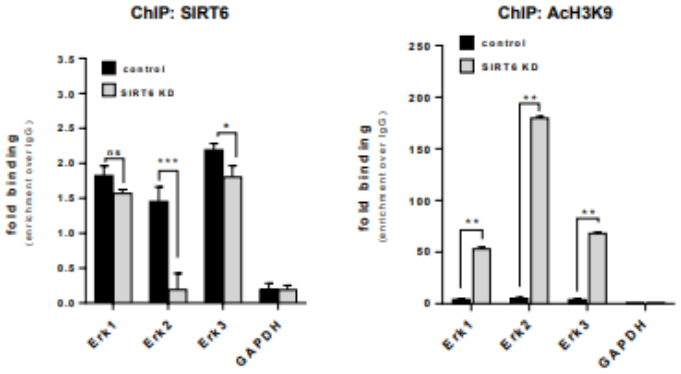

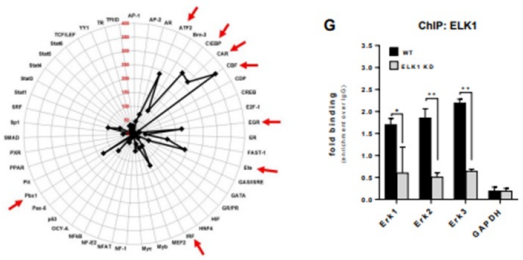

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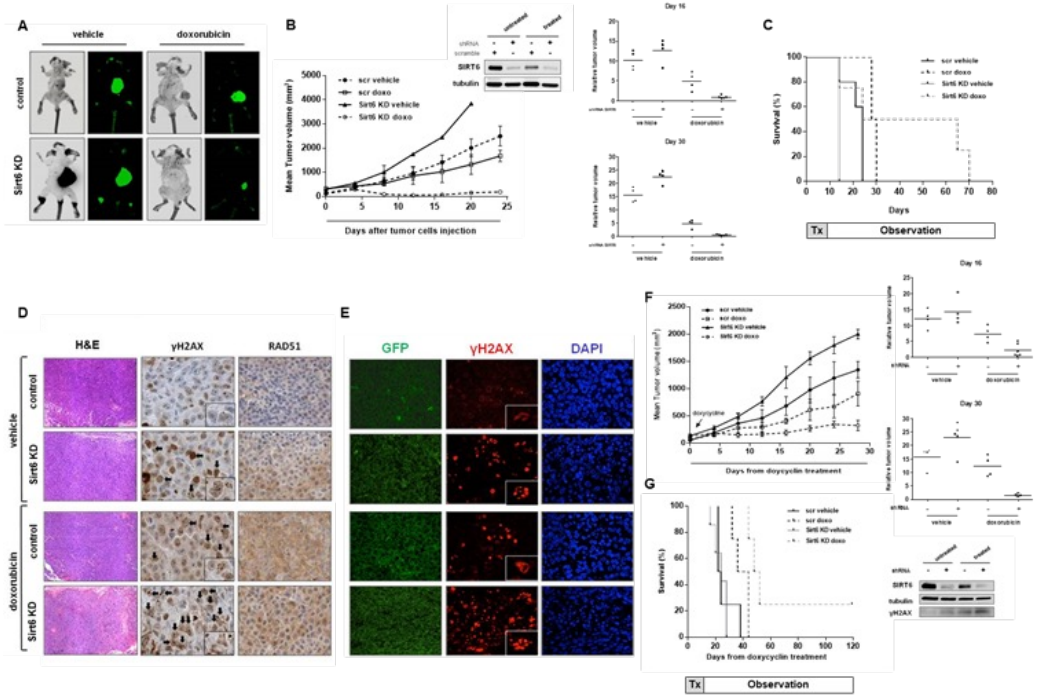
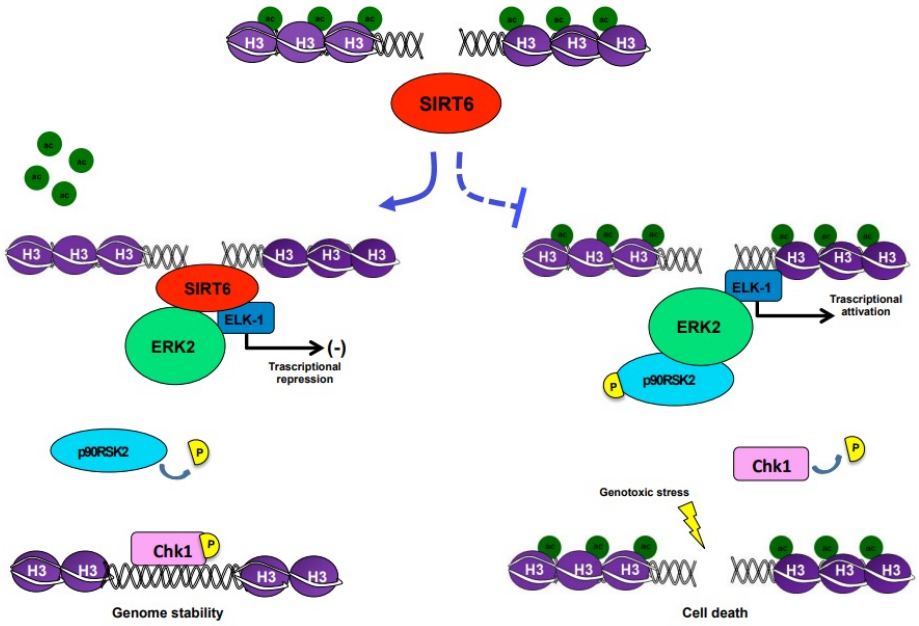
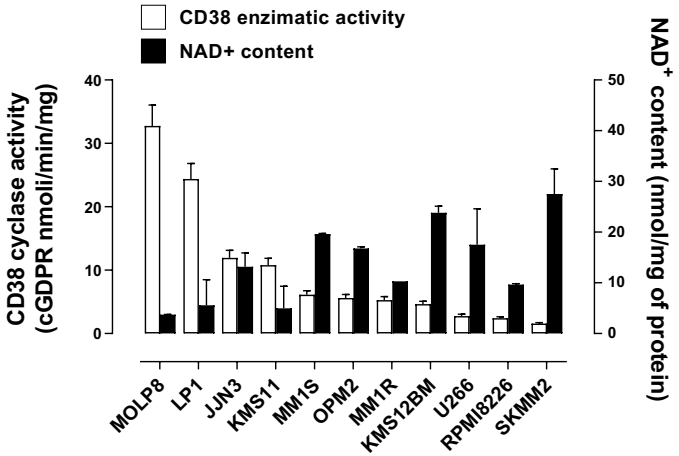
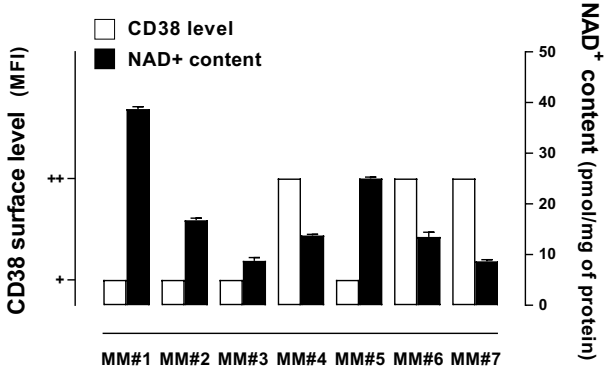


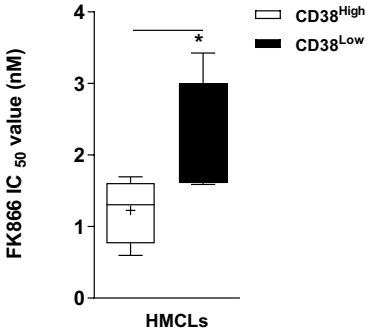


Cea M. et al. Blood 2016 Mar 3;127(9):1138-50

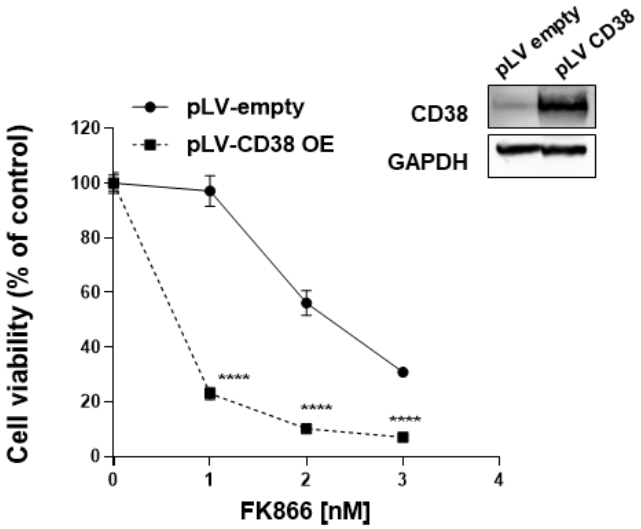
TARGETING NAD+ USERS IN MULTIPLE MYELOMA: CD38 (part II)

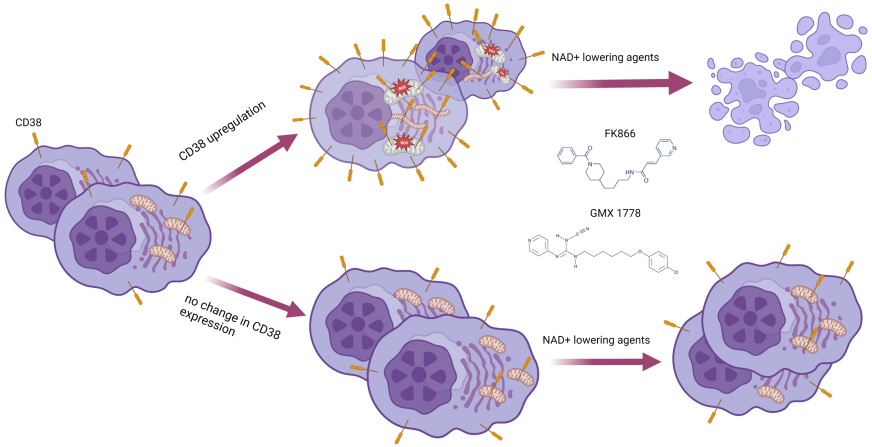






Pamela Becherini, PhD

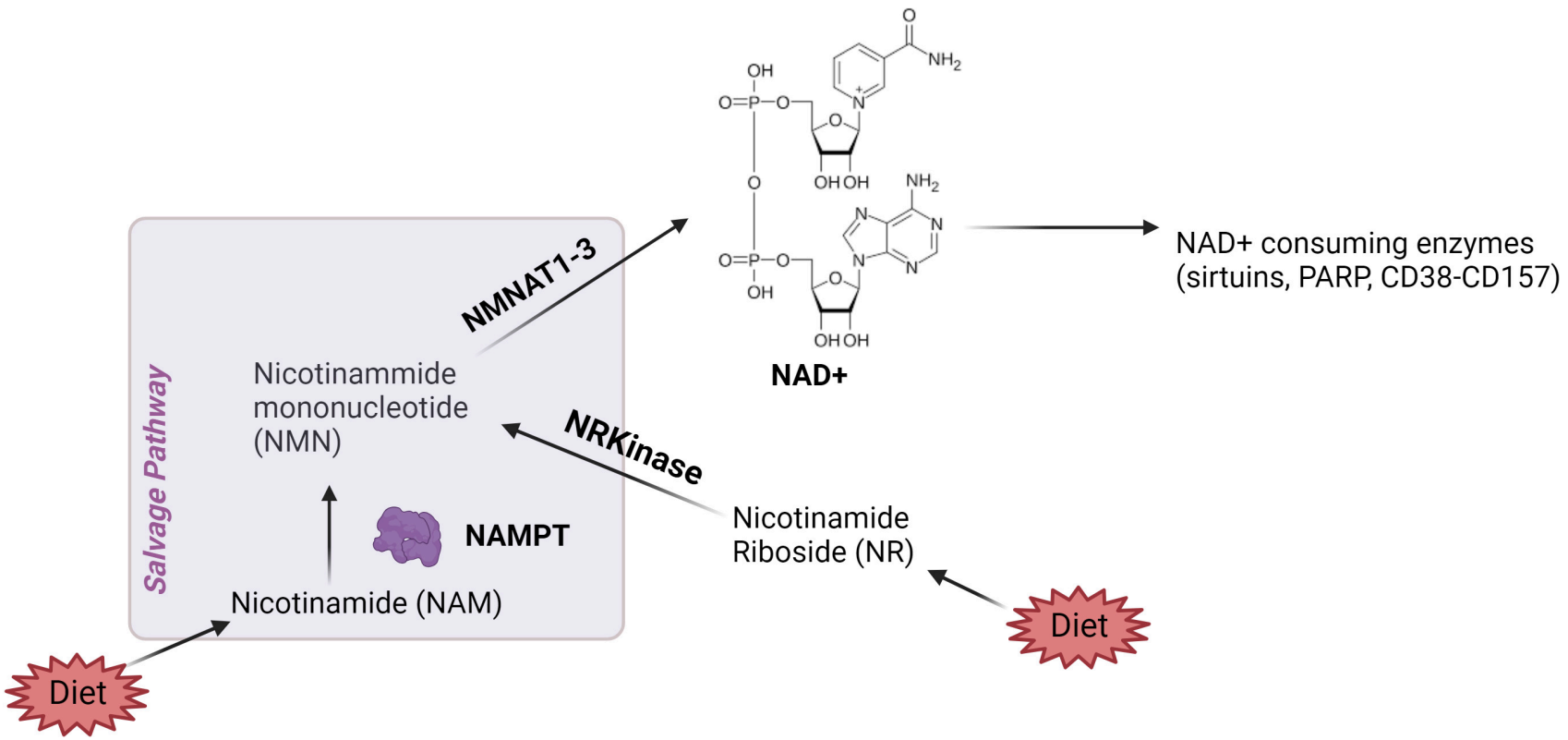




CD38-induced metabolic dysfunction primes MM cells for NAD+ lowering agents

Becherini P. et al. Antioxidants 2023 Feb 15;12(2):494

GRAPHICAL REPRESENTATION OF NAD+ BIOSYNTHETIC PATHWAYS



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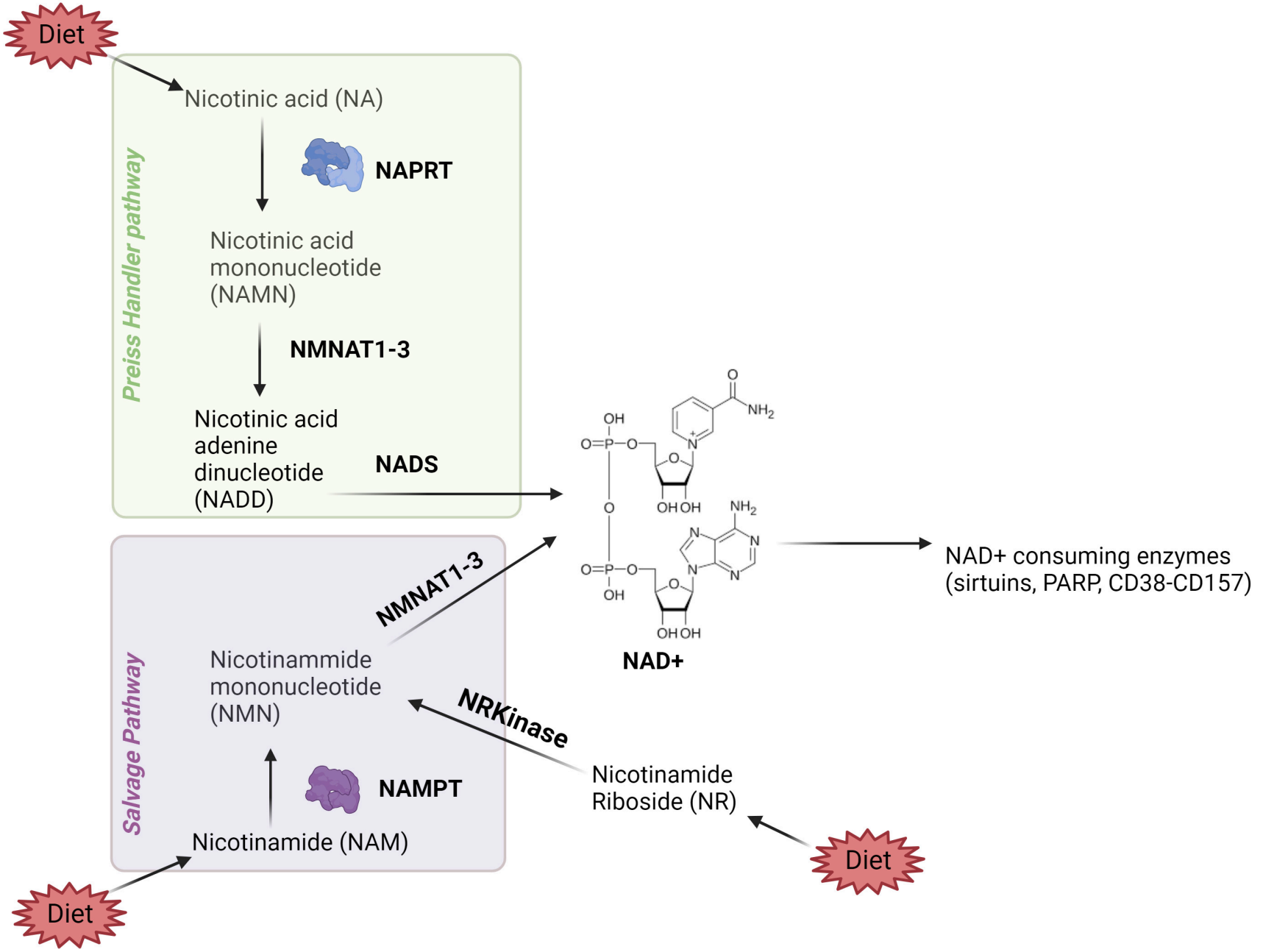

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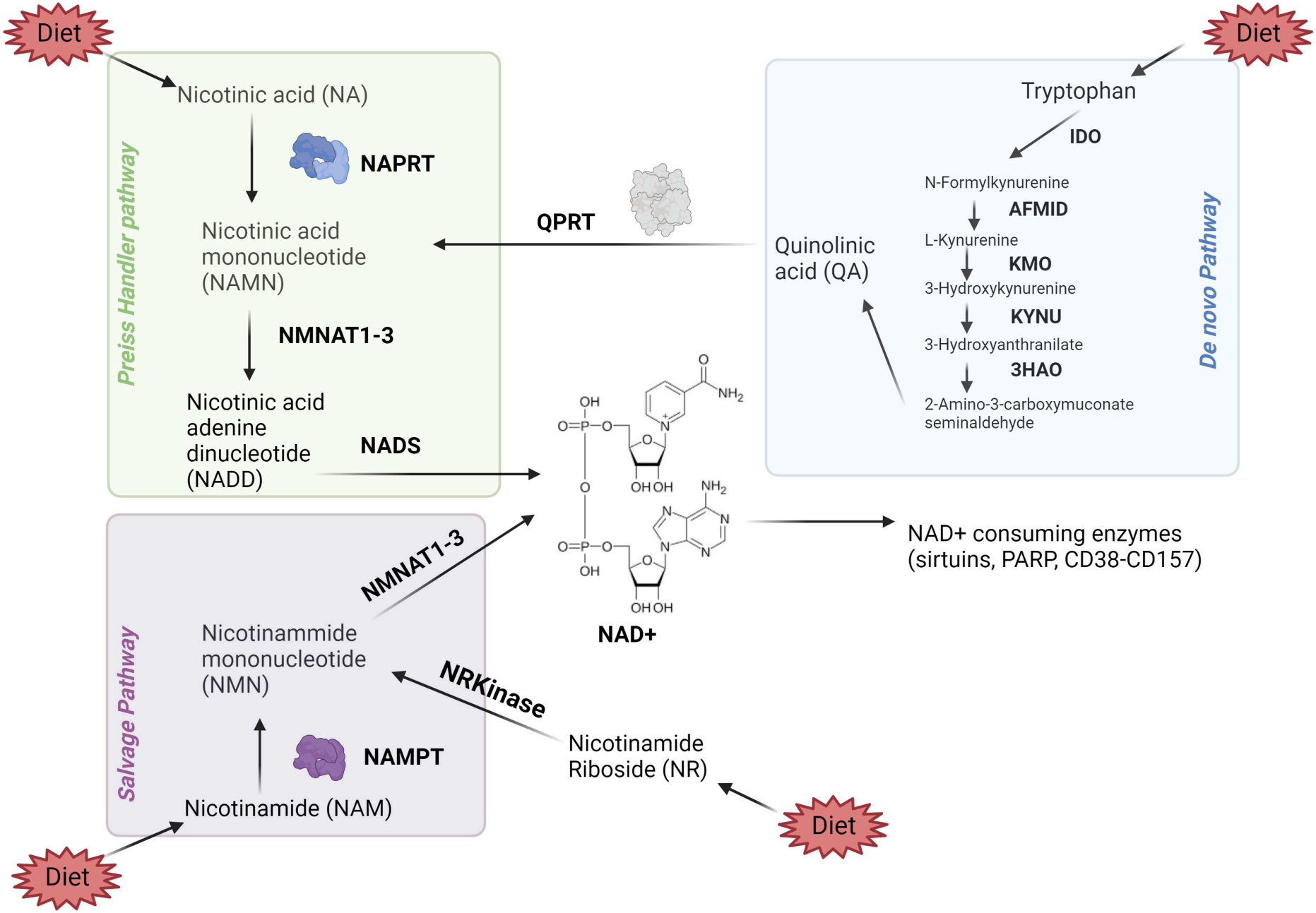
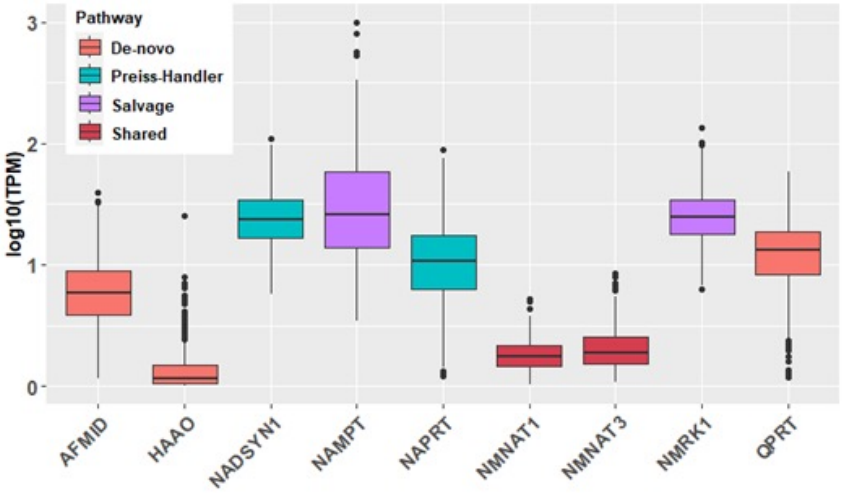
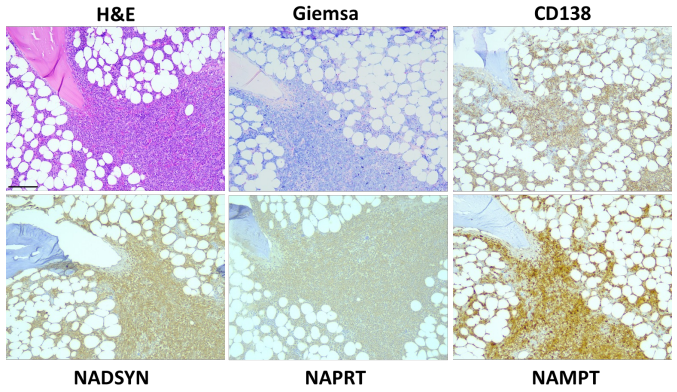
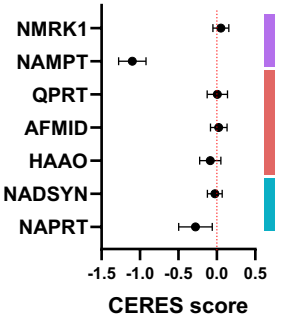
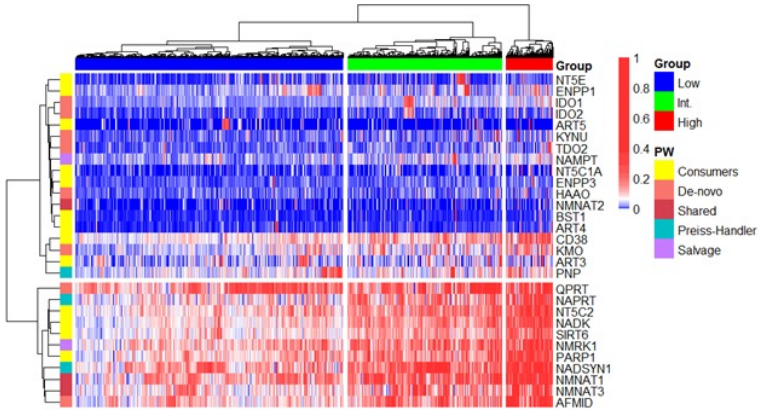


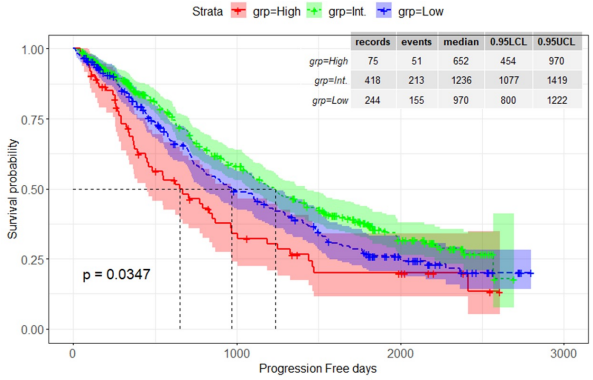
NAD+ BIOSYNTHESIS DYSREGULATION PREDICTS OUTCOME OF MM PATIENTS

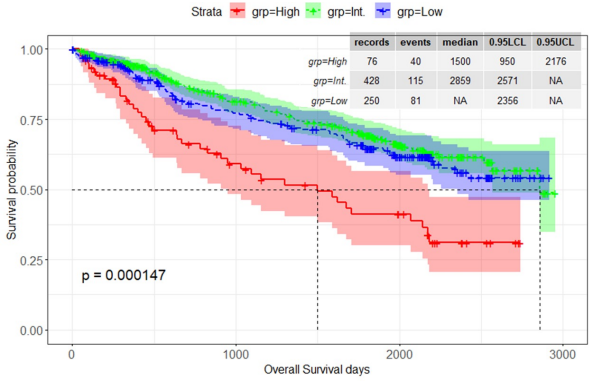








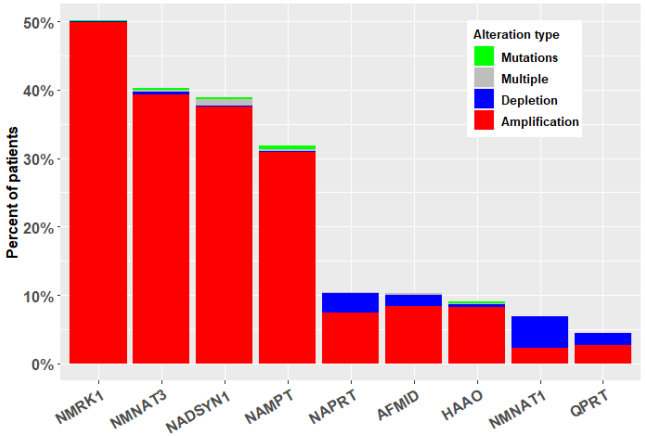


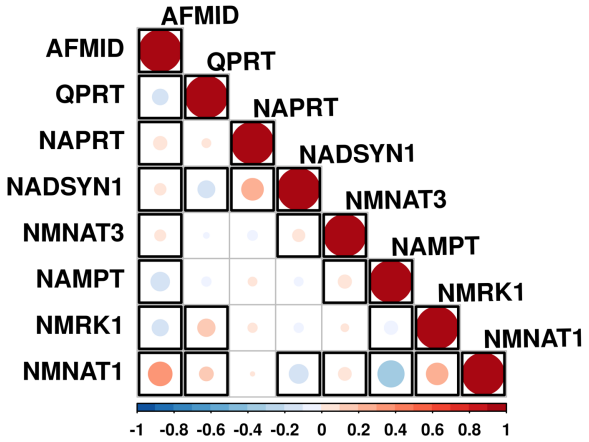


CoMMpass Analysis, Truffelli Dario, PhD

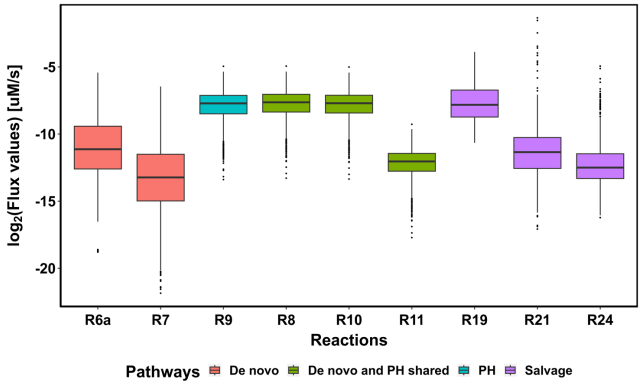
Manuscript submitted

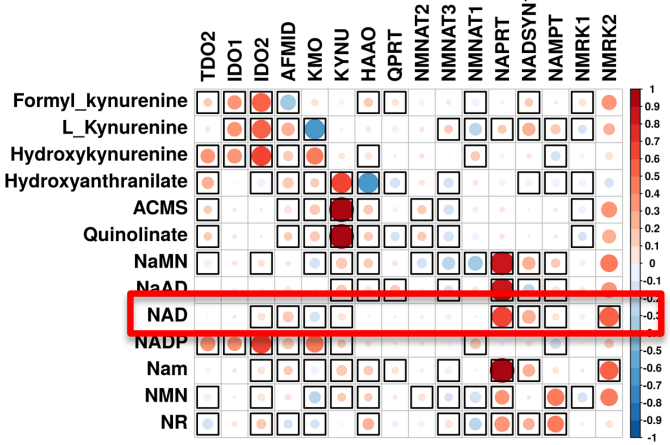
NAD⁺ BIOSYNTHESIS OF MM CELLS PREDOMINANTLY RELIES ON Preiss-Handler AND salvage- PATHWAYS

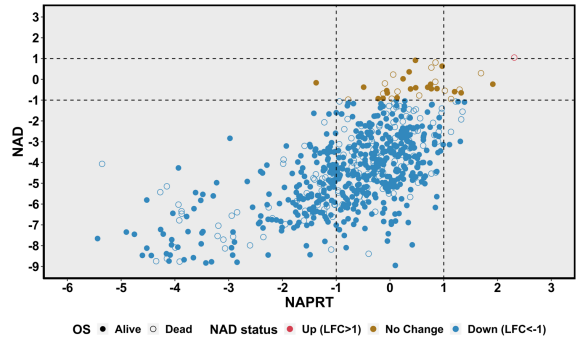




Chedere Adithya, PhD



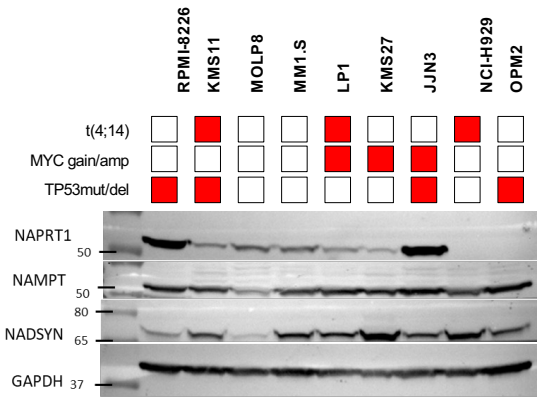


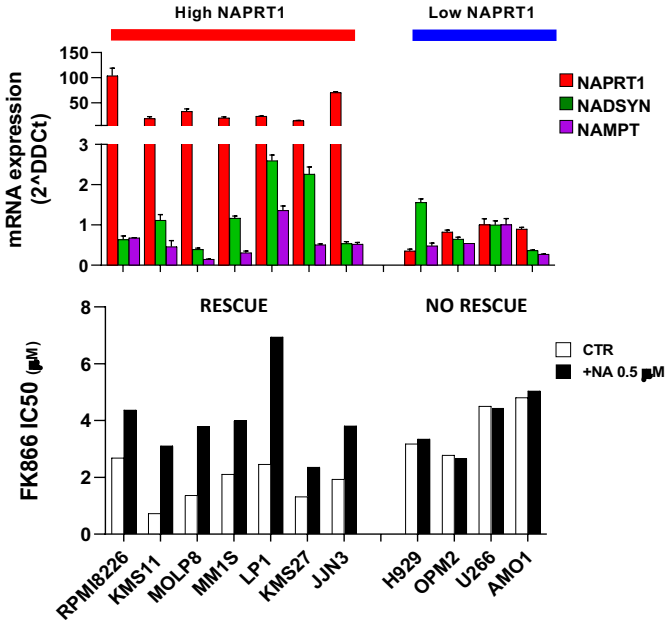


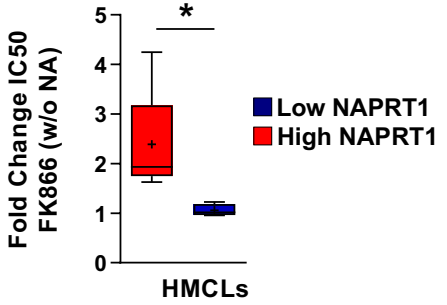
Manuscript submitted

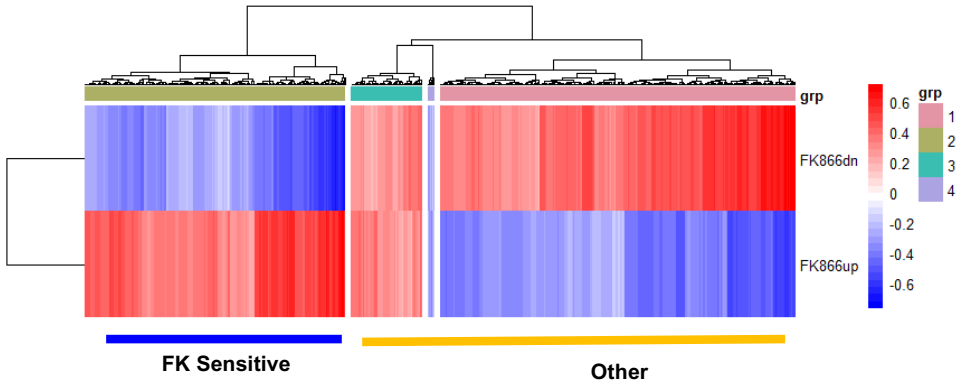
NAPRT1-TARGETING MAKES MM CELLS MORE SENSITIVE TO NAD+-LOWERING AGENTS

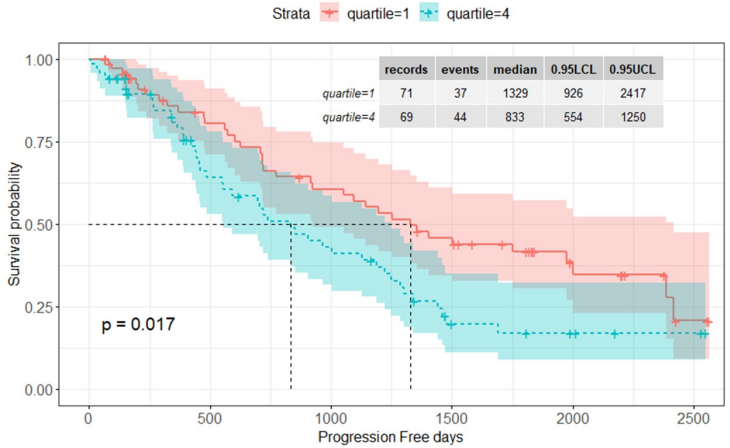
Debora Soncini, PhD







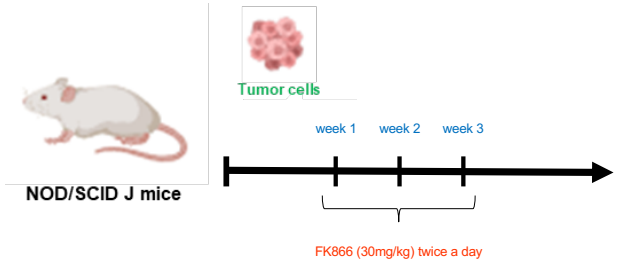


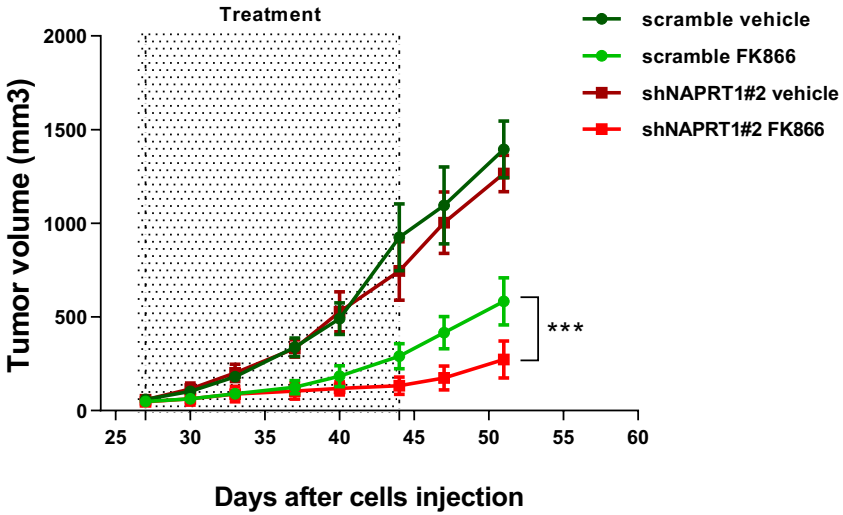


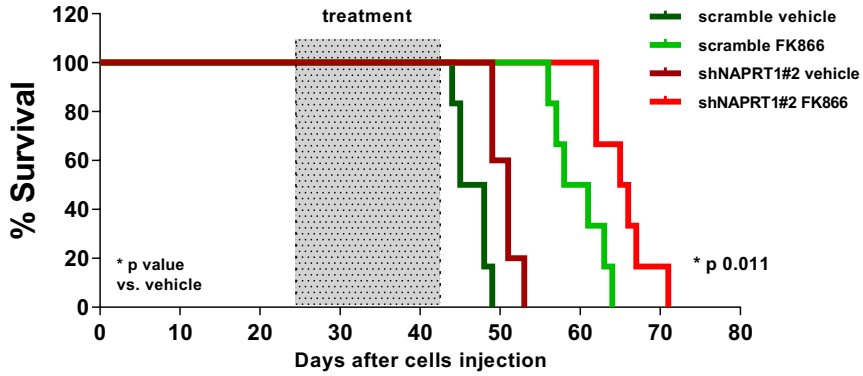
FK-sensitive signature resulted in better clinical outcome among patients with lower expression of NAPRT1 over those with higher levels

Manuscript submitted

NAPRT1 SILENCING REDUCES INTRACELLULAR NAD+ CONTENT AND SENSITIZES MM CELLS TO NAMPT-is IN XENOGRAFT MOUSE MODEL



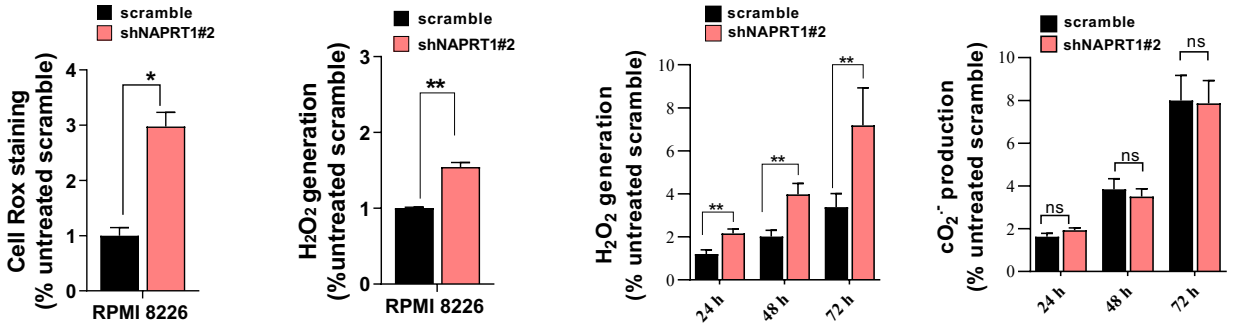




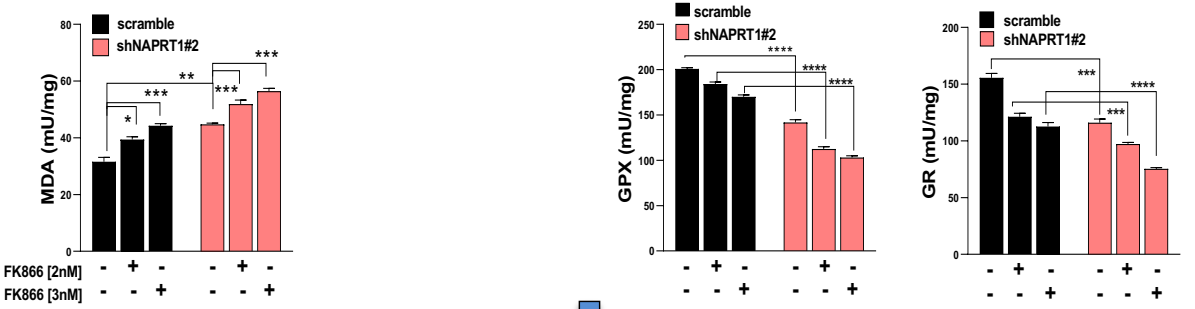
Altogether, these data support NAPRT1 modulation as a promising strategy to improve the anti-MM activity of NAMPT-is

Manuscript submitted

NAPRT1 DEFICIENCY IS ASSOCIATED WITH INCREASED OXIDATIVE STRESS IN MM CELLS

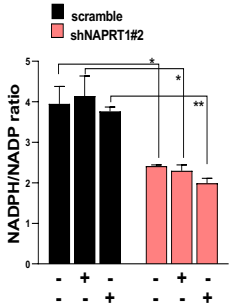


NAPRT1-depleted tumors have high ROS content



OXIDATIVE STRESS BIOMARKER

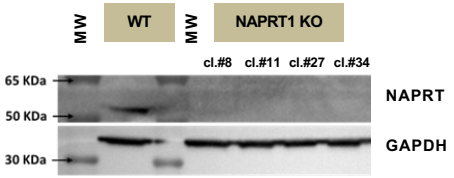
ENDOGENOUS ANTIOXIDANT DEFENSES

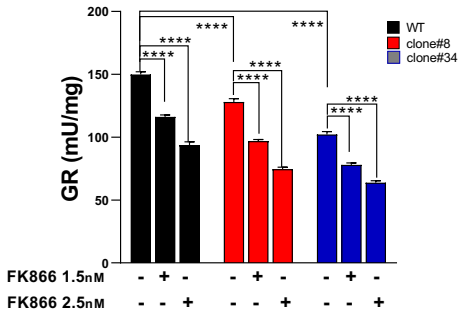


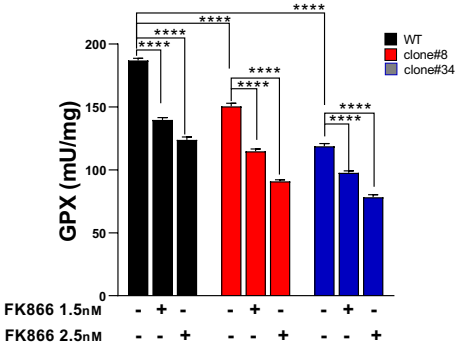
……..NAPRT1 silencing results in impaired efficacy of the redox homeostasis mechanisms in MM cells

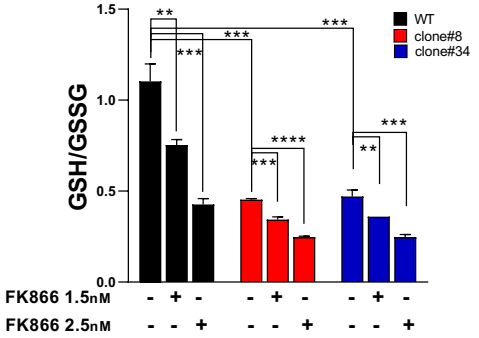
NAPRT1 ACTIVITY IS CRUCIAL FOR REDOX HOMEOSTASIS AND OXIDATIVE METABOLISM OF MM CELLS

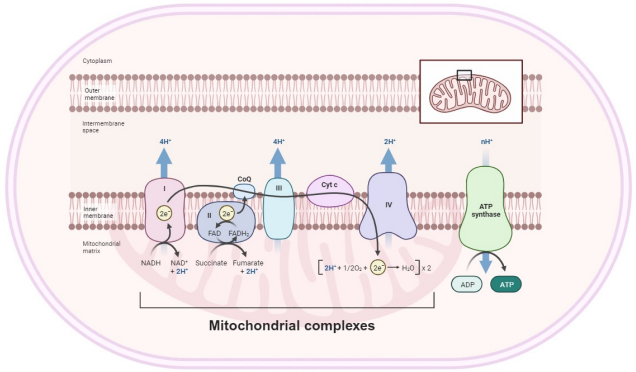
Francesco Ladisa, PhD student

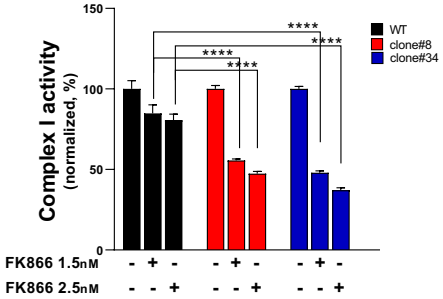


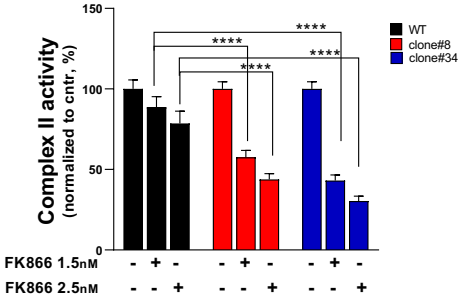


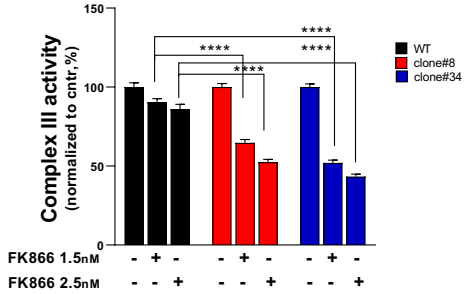


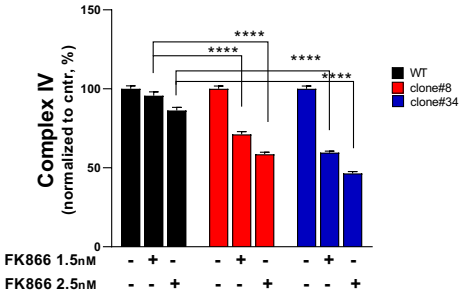






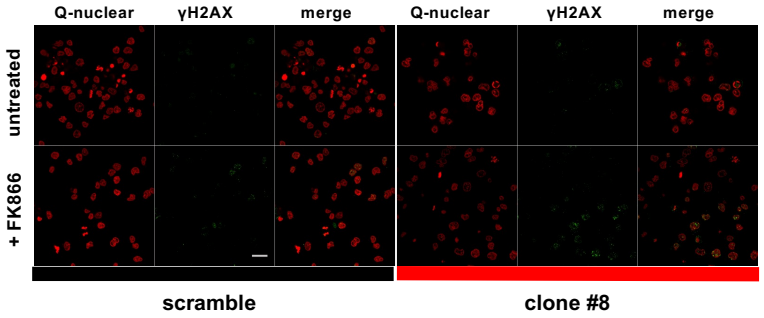


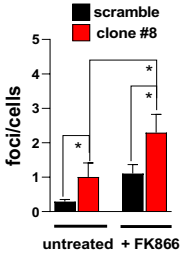


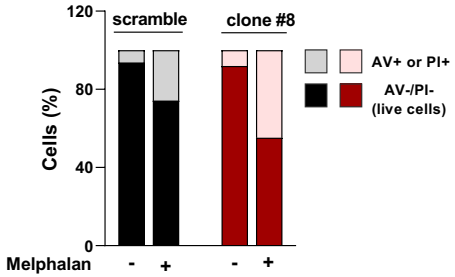


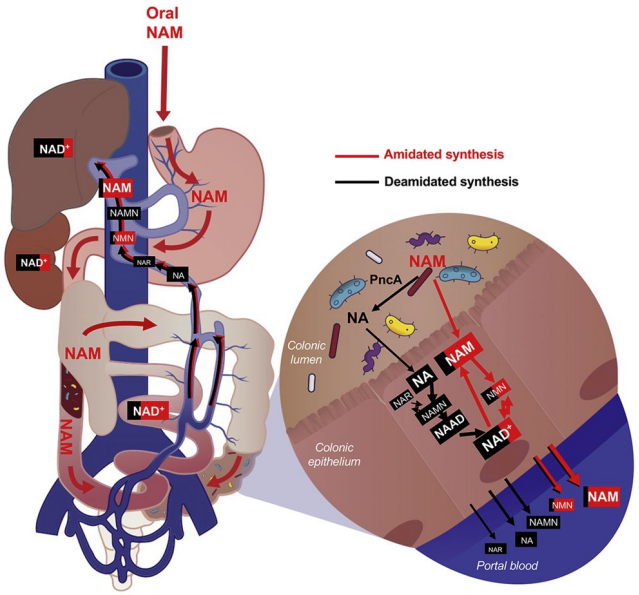
Manuscript submitted

GUT-MICROBIOTA TARGETING RESULTS IN ENHANCED HDM-BASED PROGRAMS EFFICACY IN TE-MM PATIENTS

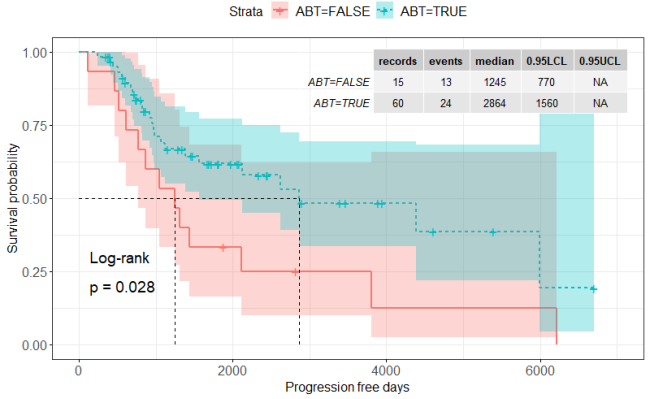


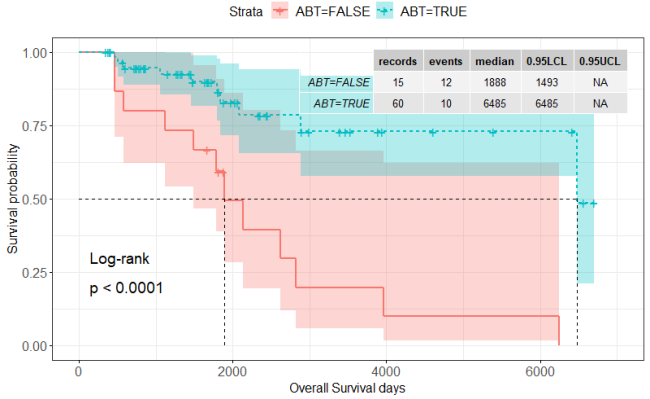






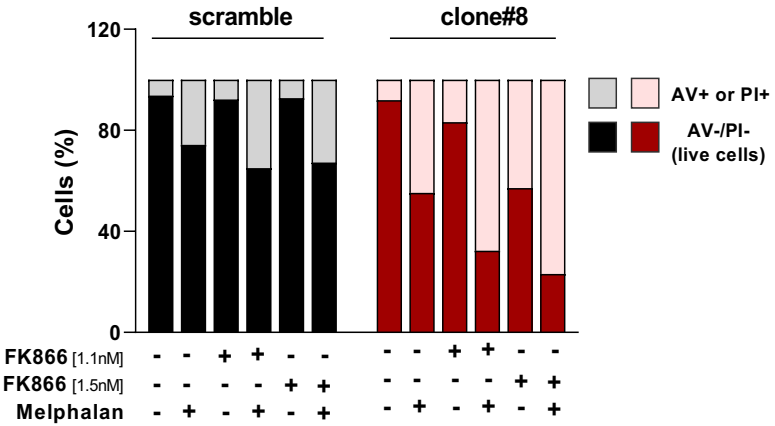
Shats I. et al Cell Metabolism 2020 Mar 3;31(3):564-579.

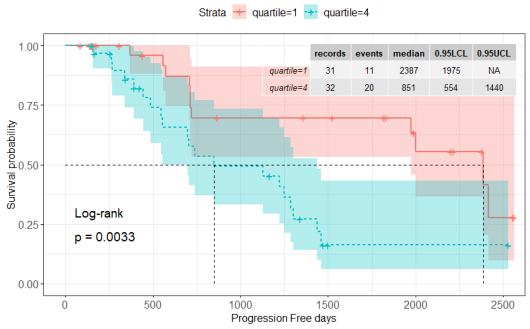


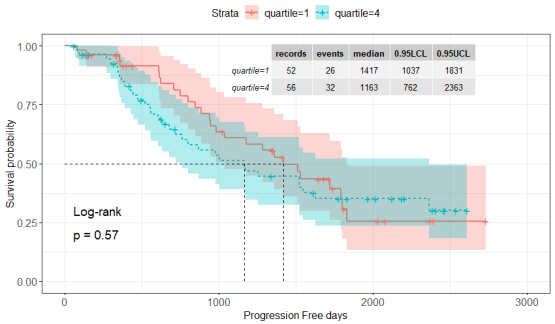


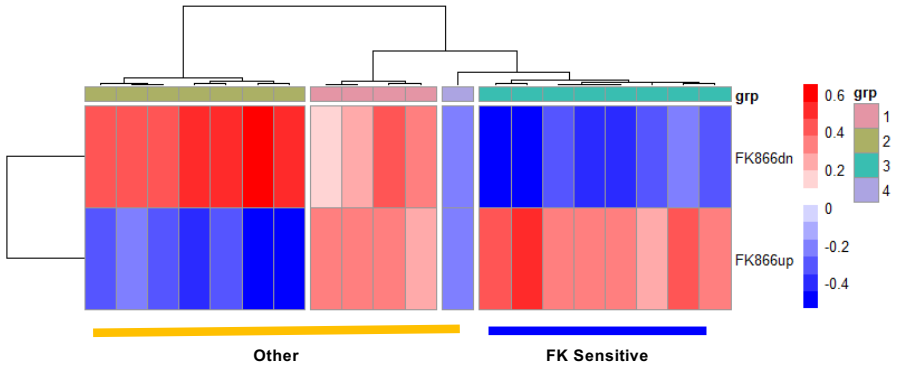
Manuscript submitted

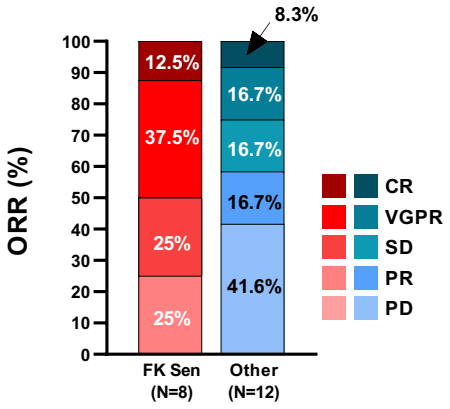
NAD+ METABOLISM RESTRICTION BOOSTS HIGH-DOSE MELPHANAN EFFICACY IN MULTIPLE MYELOMA PATIENTS

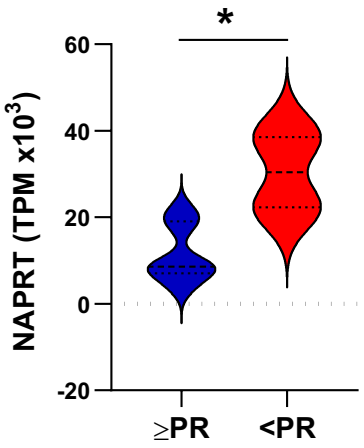












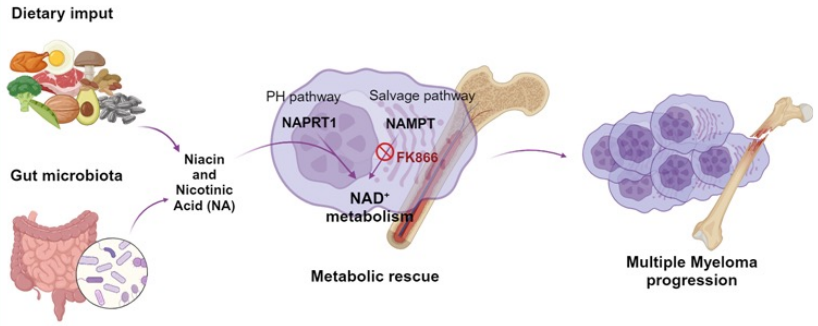
……complete NAD⁺-starvation is likely to improve the efficacy of HDM-based regimens.

Manuscript submitted

NAD+ METABOLISM RESTRICTION BOOSTS HIGH-DOSE MELPHANAN EFFICACY IN MULTIPLE MYELOMA PATIENTS

WORKING HYPOTHESIS

1.



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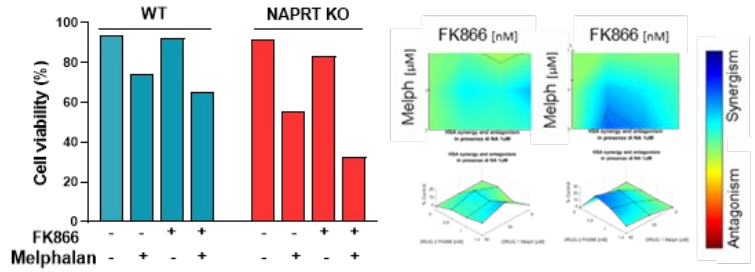

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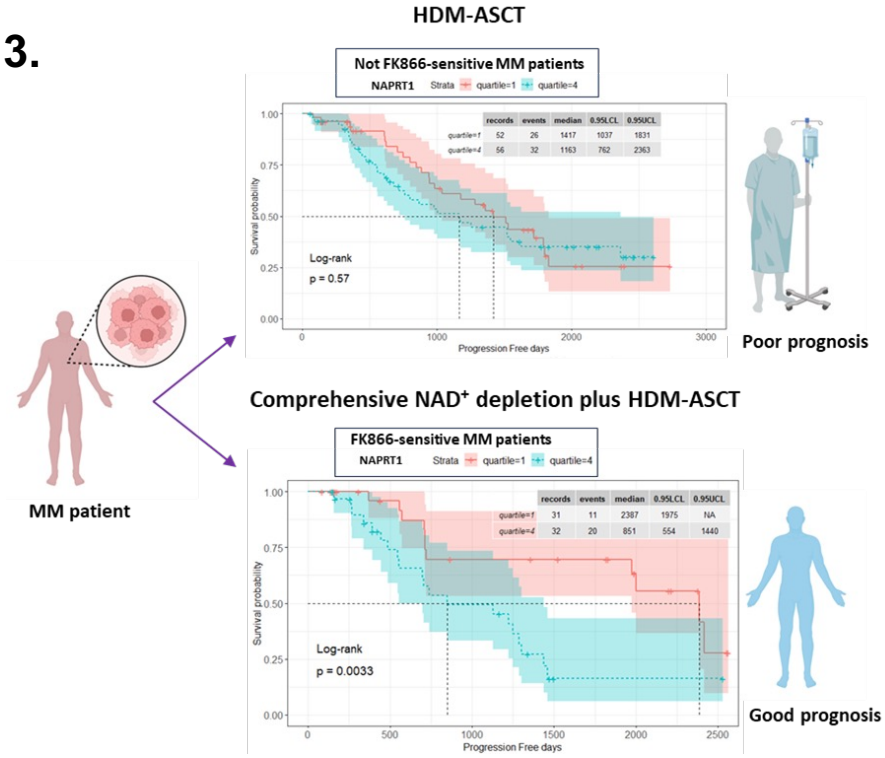

The complete NAD⁺-starvation, as obtained through combined NAPRT1 and NAMPT inhibition, improves prognosis of TE-NDMM patients

SUMMARY AND UNMET NEED

- **Metabolic reprogramming** is a hallmark of human cancer and represents a non-oncogene addiction for cell growth, survival, proliferation, and long-term maintenance

- **Metabolic dysregulation** makes MM cells particularly vulnerable to anti-MM treatments thus supporting relevance of metabolism-targeting approaches in this tumor.

- The **NAD^+ landscape** of MM cells furnishes basis for its targeting (SIRTuins, CD38, PARPs or biosynthesis enzymes) to screen novel strategies, allowing thus to achieving an improvement of MM clinical prognosis.

- NAD^+-focused restriction resulting from **NAMPT/NAPRT1 dual inhibition** represents an intriguing avenue for exploiting effectiveness of HDM-based regimens and also provides a novel biomarker to predict efficacy of these programs.

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