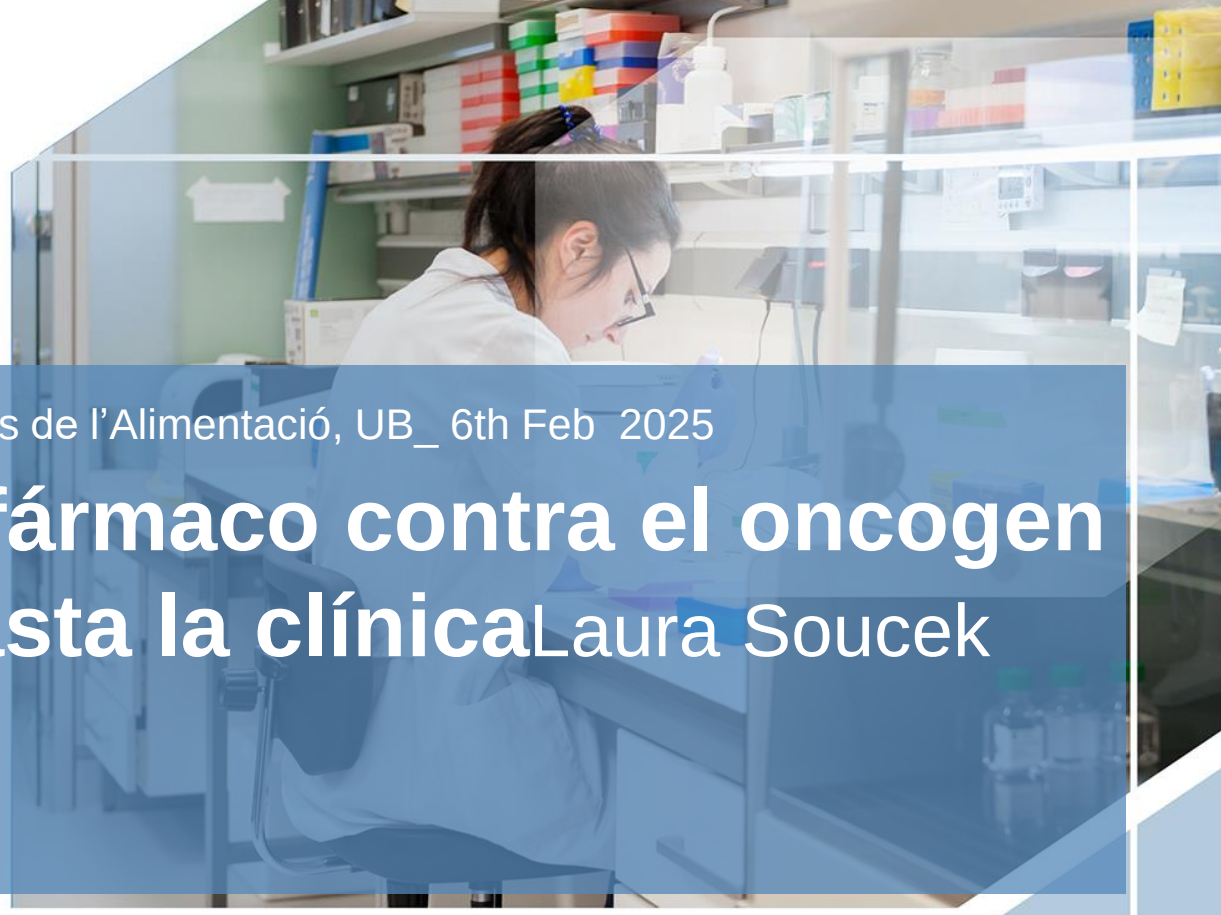


Seminars de Recerca i Tecnològics_Facultad de Farmacia i Ciencies de l'Alimentació, UB_ 6th Feb 2025

El desafío del desarrollo de un fármaco contra el oncogen MYC: desde el laboratorio hasta la clínica

Laura Soucek

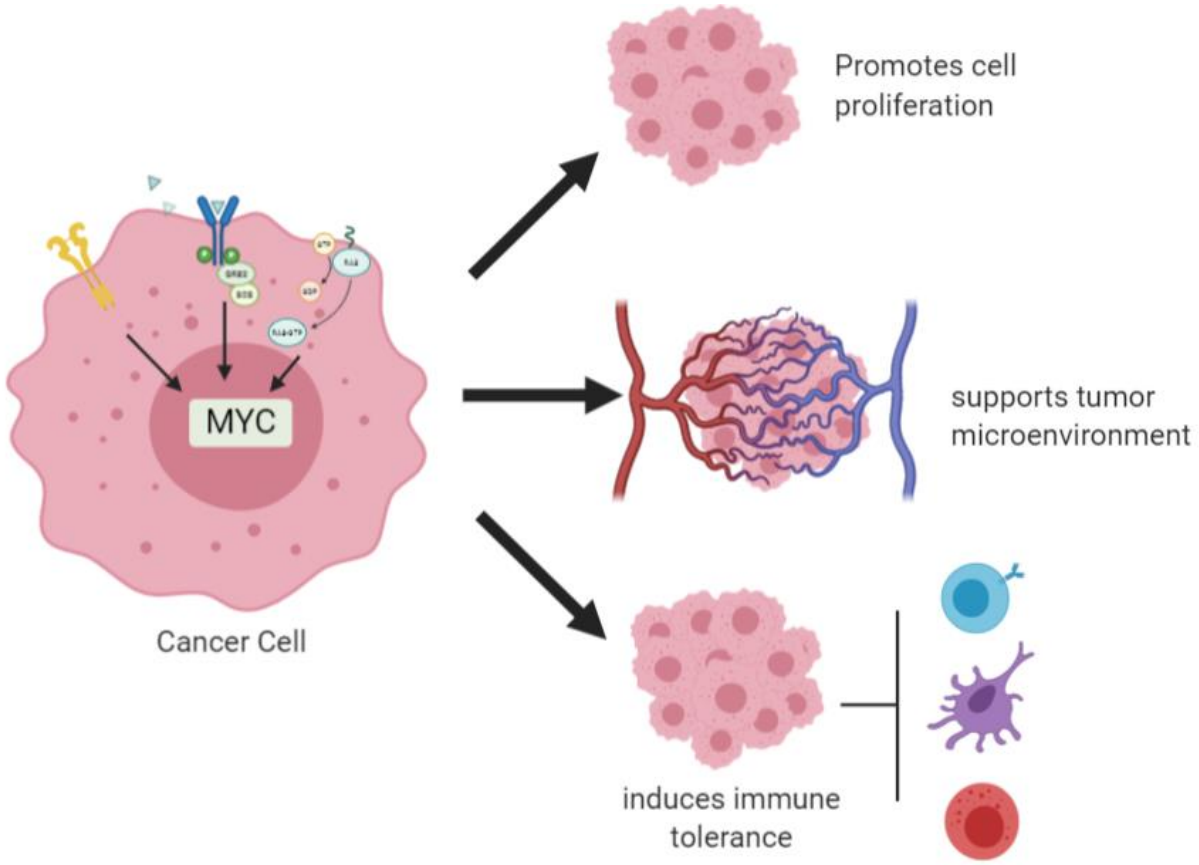
ICREA Research Professor
Models of Cancer Therapies Laboratory
Vall d'Hebron Institute of Oncology (VHIO)
Co-founder and CEO of Peptomyc

PEPTOMYC

ICREA

VHIO VALL D'HEBRON Institute of Oncology

OUR FOCUS: MYC, THE MOST DEREGULATED ONCOGENE IN HUMAN CANCER

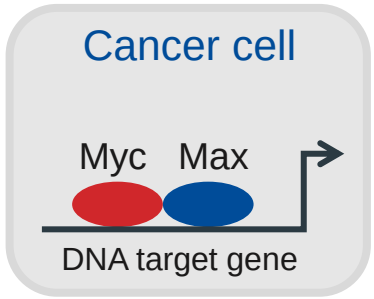


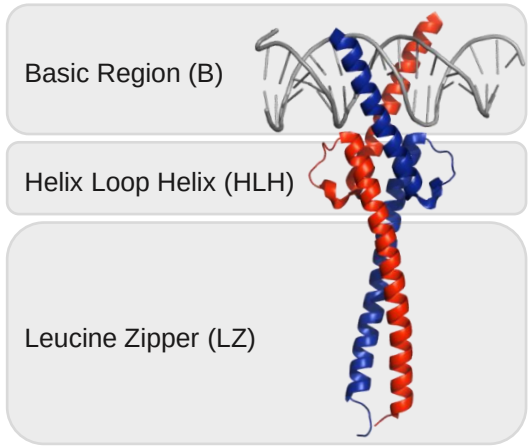
GROWTH AND SURVIVAL TO TREATMENTS

Issues:

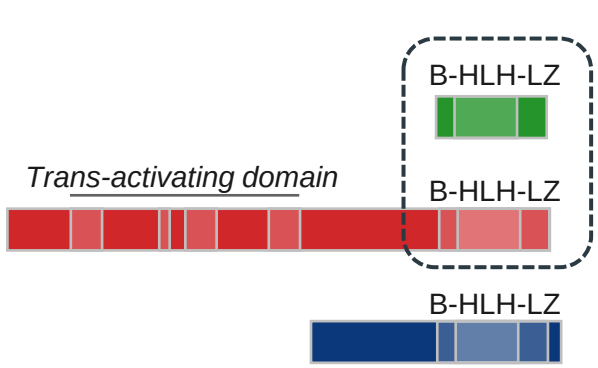
1. Intrinsically disordered protein
2. It resides in the nuclei
3. It does not have an active site
4. Multiple Myc proteins (c-, N- & L-)
5. Needed for normal tissue maintenance

OUR MAIN TOOL: OMOMYC





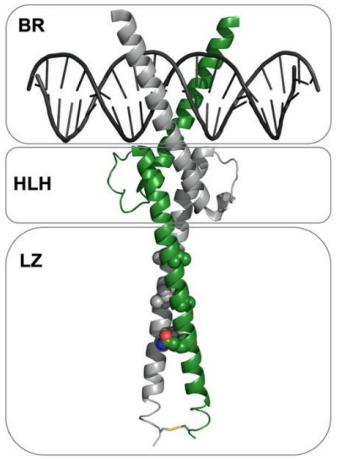
Crystal structure of the B-HLH-LZ of c-Myc/Max
(Nair & Burley, 2003)

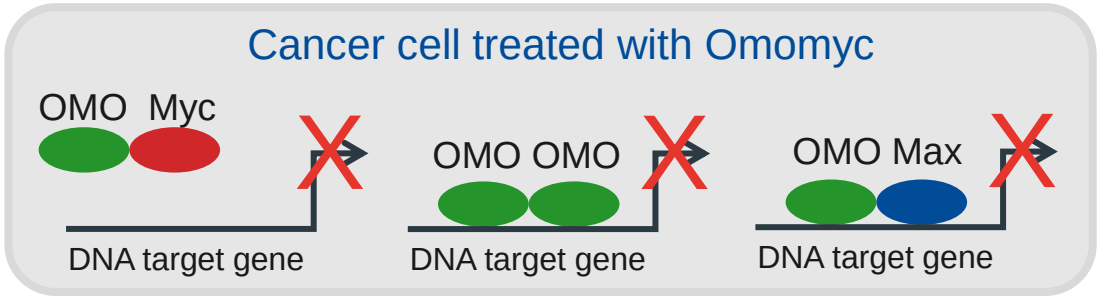


Omomyc

c-, N-, L-Myc

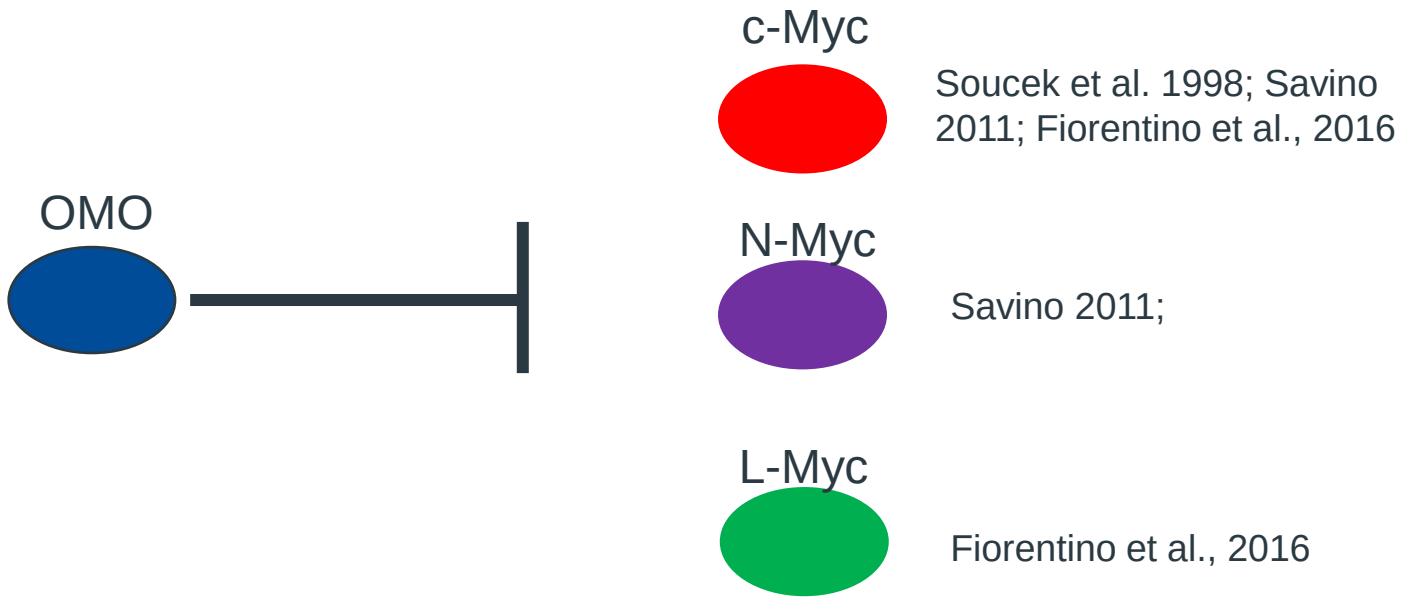
p21/p22 Max



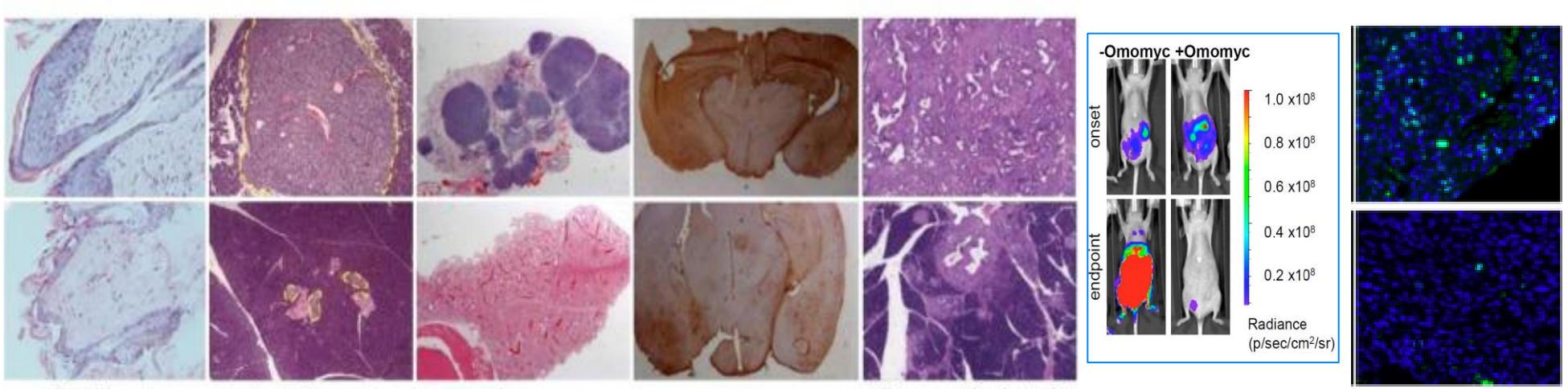


- Shutdown of MYC transcriptional signature
- Cell cycle arrest and death of tumor cells

OMOMYC AS A PAN-MYC INHIBITOR



THE OPPORTUNITY TO ATTACK DIFFERENT TYPES OF CANCER



Soucek et al., Cell Death & Diff 2004

Sodir et al., Genes & Dev 2011

Soucek et al., Nature 2008; Soucek et al., Genes & Dev 2013

Annibali et al., Nat Comm 2014

Sodir et al., Cancer Disc 2020

Massó-Vallés et al., Cancer Res Comm 2022

Zacarias-Fluck et al., Genes & Dev 2023

All secondary effects are mild and completely reversible;
unexpected and excellent therapeutic window

Masso-Vallés 2020

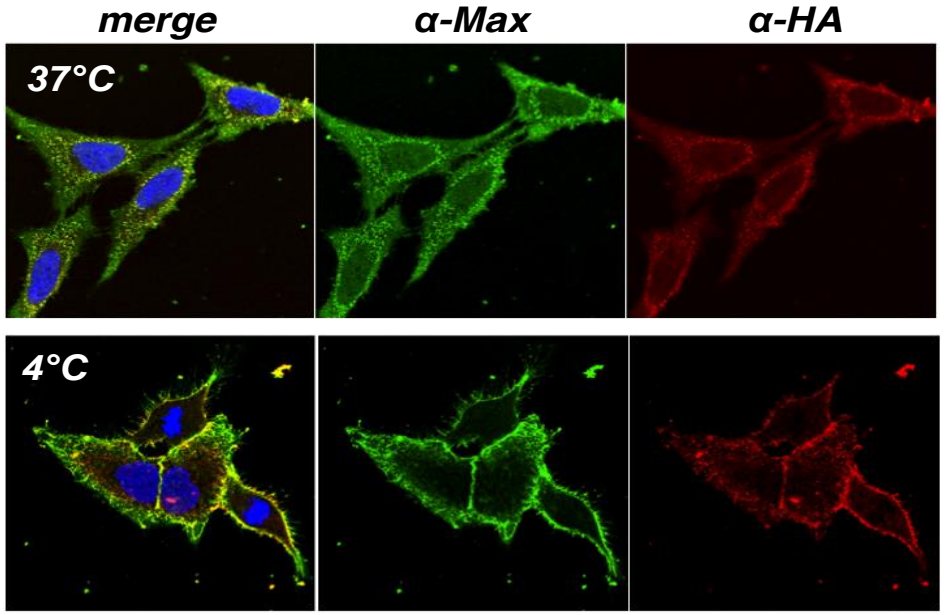
CAN OMOMYC BE A DRUG?

The biggest challenge: “It is a molecule too big and bulky to be directly delivered to cells”.

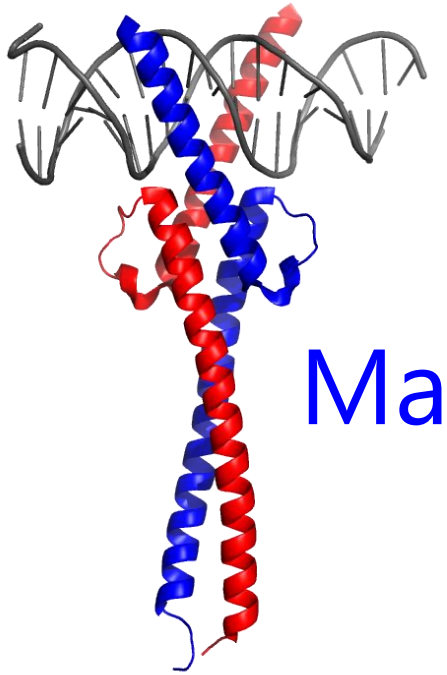
“Omomyc is essentially just a proof of concept and can only work as gene therapy.”

BREAKTHROUGH:

Montagne, M., Beaudoin, N., Fortin, D., Lavoie, C. L., Klinck, R., and Lavigne, P. (2012) The Max b-HLH-LZ (Max*) can transduce into cells and inhibit c-Myc transcriptional activities, PLoS One 7, e32172.

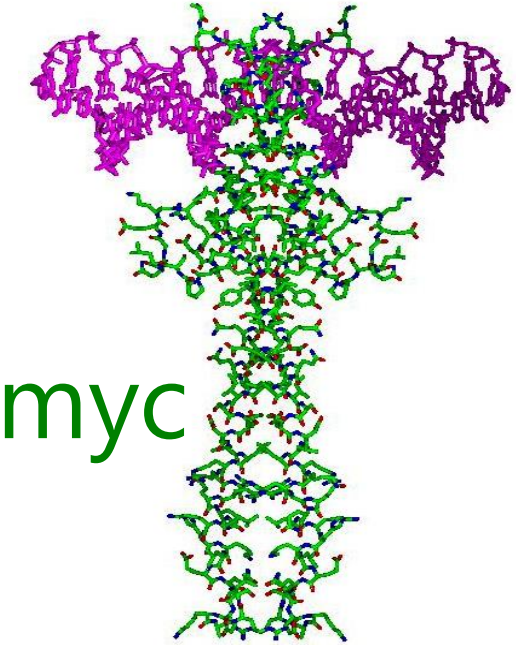


FIND THE DIFFERENCES

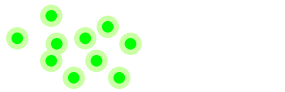


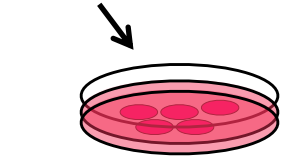
Max*

Omomyc

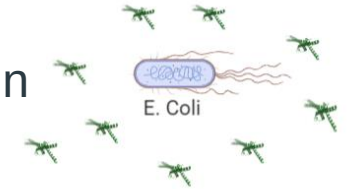


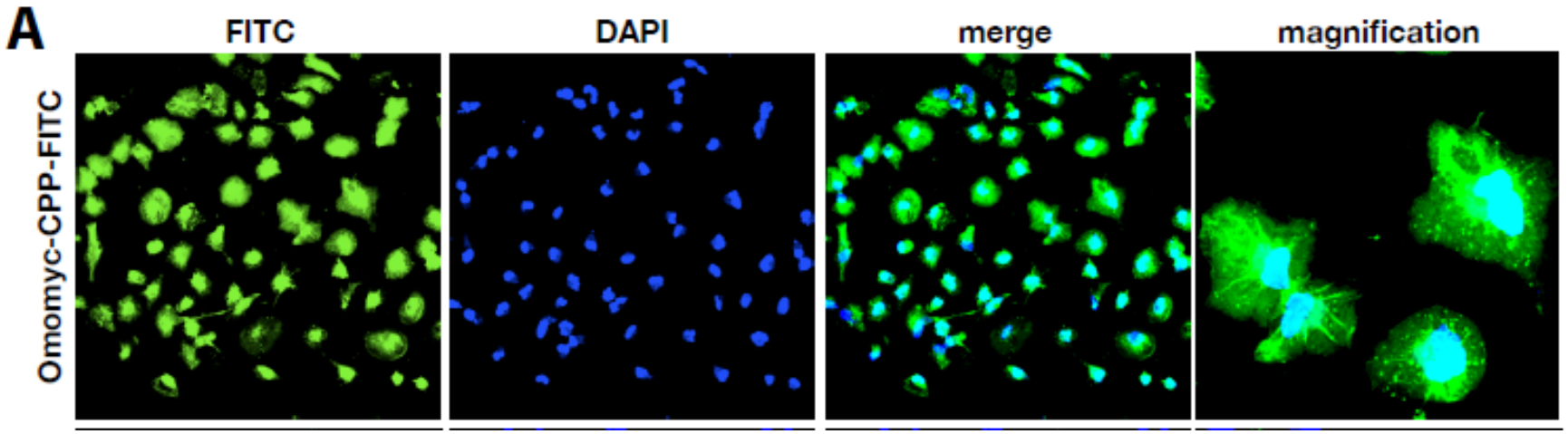
THE SURPRISE: OMOMYC WORKS AS A CELL PENETRATING PEPTIDE





Recombinant protein

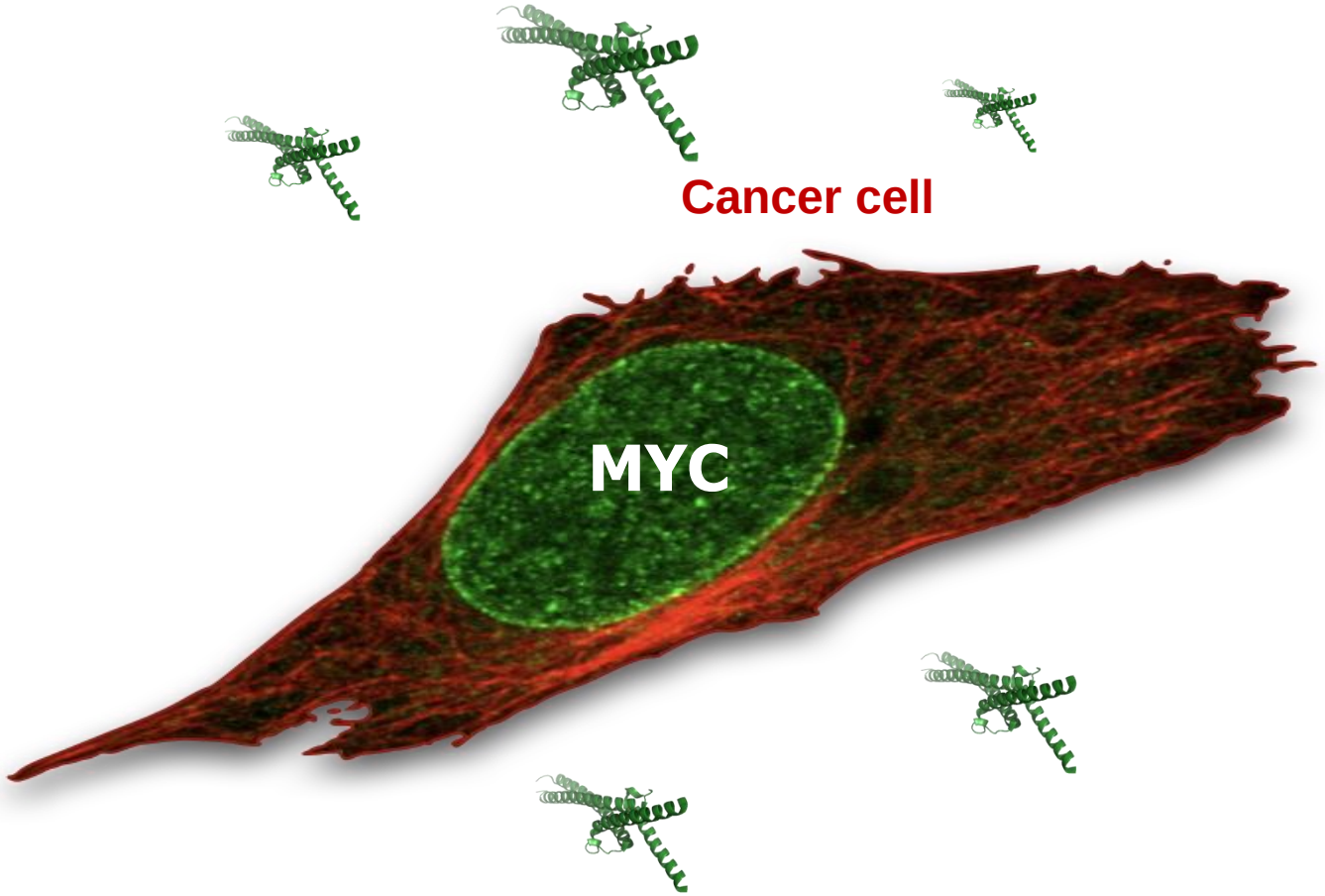




A549 cells treated with Omomyc-FITC peptide (12,8 μM, 20')

Beaulieu et al., 2019

OMOMYC-DERIVED PEPTIDES AS PHARMACOLOGICAL TOOLS



PEPTOMYC

We founded Peptomyc

December 2014

Founders:

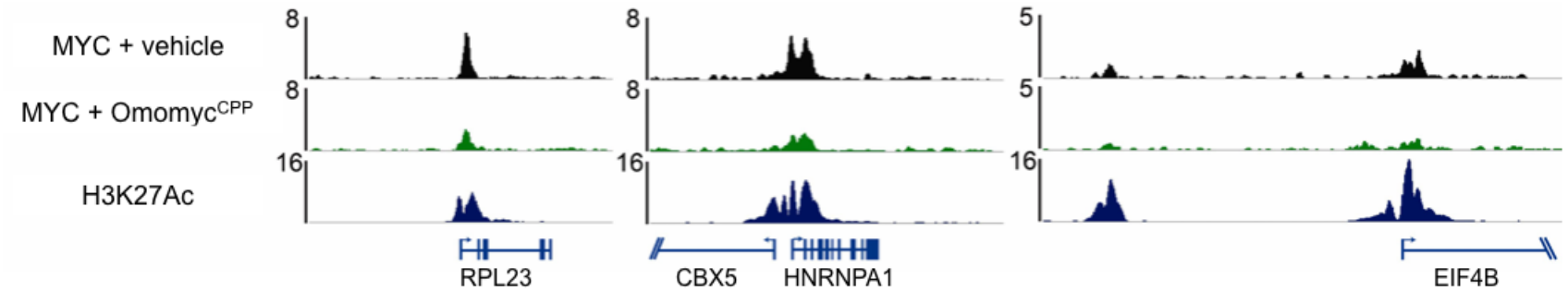
Laura Soucek

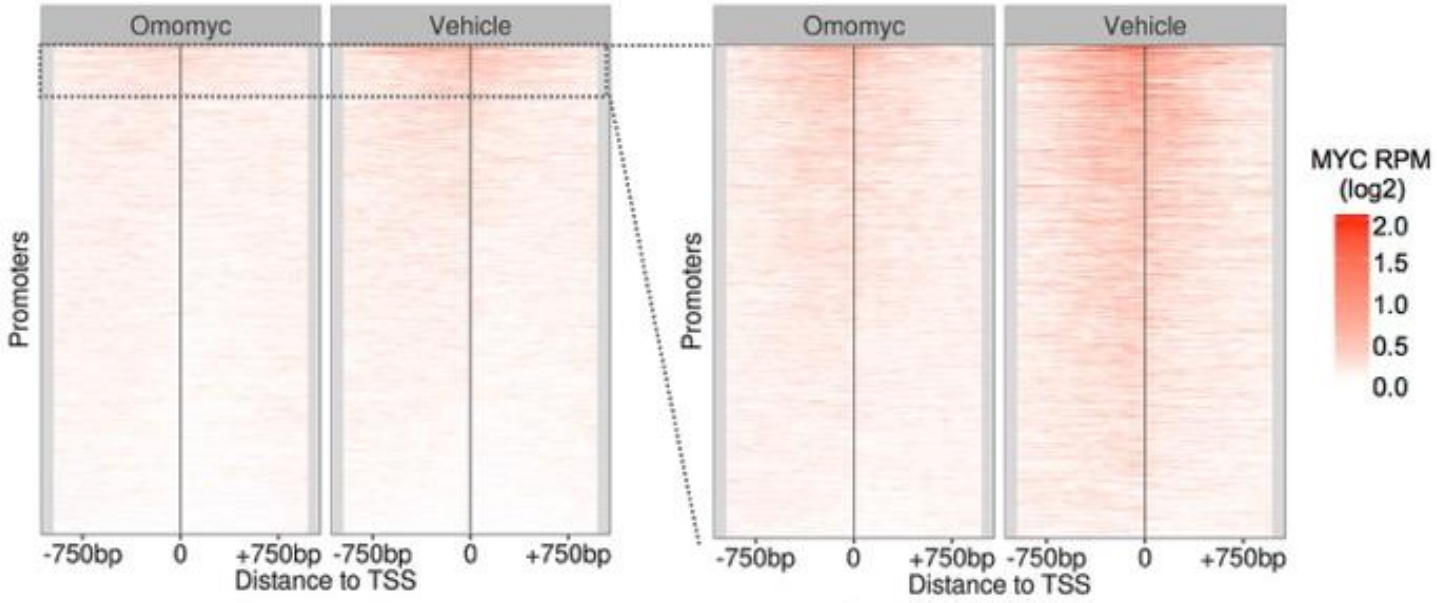
Marie-Eve Beaulieu

VHIO

ICREA

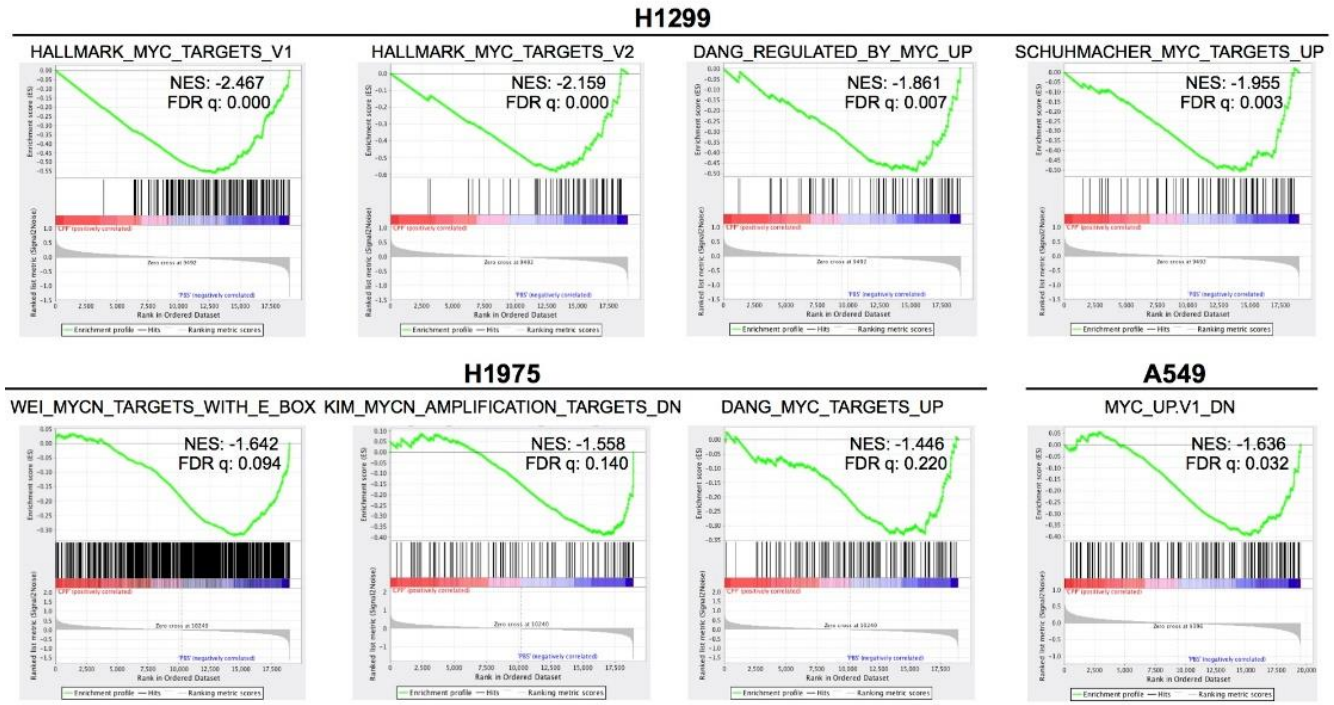
THE OMOMYC MINI-PROTEIN DISPLACES MYC FROM DNA





Beaulieu et al., 2019

THE OMOMYC MINI-PROTEIN SHUTS-DOWN MYC TRANSCRIPTIONAL SIGNATURE

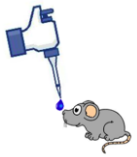


Beaulieu et al., 2019

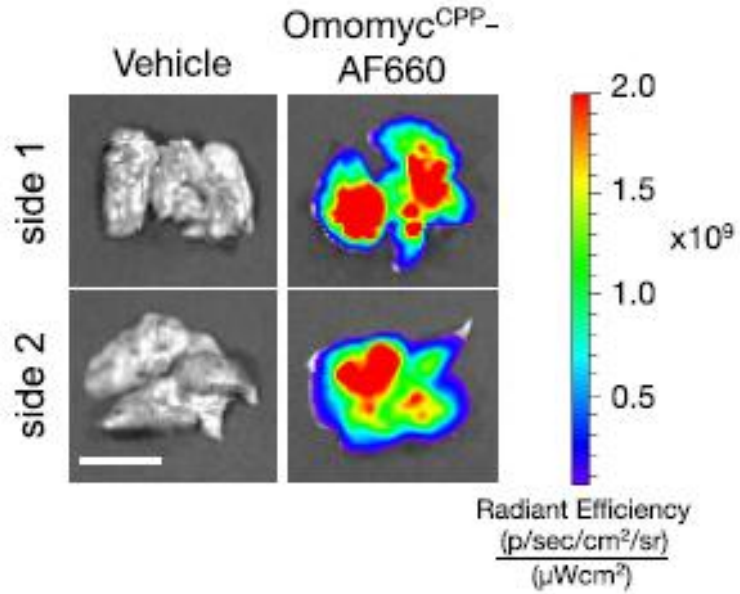
No other bHLHZ TFs are affected instead

		H1299		H1975		A549	
Gene set from the TFTs collection	**n**	**NES**	**FDR q-val**	**NES**	**FDR q-val**	**NES**	**FDR q-val**
ARNT_01	237	1.00754	0.61460	1.25461	0.39636	-0.81194	1.00000
ARNT_02	230	0.94980	0.75035	-0.88402	0.93081	0.68568	1.00000
NFY_01	239	-1.12758	0.54262	-1.11955	0.63275	-0.92765	0.87500
NFY_C	233	-1.11319	0.57269	-0.84240	0.98602	0.96401	1.00000
NFY_Q6	248	-1.11209	0.56933	-1.08287	0.66406	-1.11064	0.50783
NFY_Q6_01	249	-1.28062	0.26962	-1.25756	0.31640	-0.95921	0.82760
SMAD4_Q6	235	1.10137	0.42661	-0.94367	0.85693	-1.09693	0.52207
STAT1_01	63	0.70864	1.00000	0.94980	0.82137	-1.23418	0.31982
STAT1_02	238	-0.91835	1.00000	-0.75506	1.00000	-0.94637	0.84515
STAT1_03	232	-0.78809	1.00000	0.76156	0.99734	-1.08119	0.55720
USF_01	235	-0.81321	1.00000	-1.19457	0.47306	-0.71077	1.00000
USF_02	257	-0.92457	1.00000	1.02514	0.71879	0.76161	1.00000
USF_C	262	0.88533	0.86546	1.18836	0.46144	0.85170	1.00000
USF_Q6	243	-0.82074	1.00000	-0.80391	1.00000	-0.72776	1.00000
USF_Q6_01	220	1.01892	0.59415	1.08449	0.63940	-0.69480	1.00000
YY1_01	233	0.80373	0.97280	-0.93414	0.86782	-0.86355	0.98040
YY1_02	228	-1.04733	0.72844	-1.37800	0.16307	-0.54340	1.00000
YY1_Q6	223	-0.86007	1.00000	-1.44888	0.09191	0.61990	1.00000

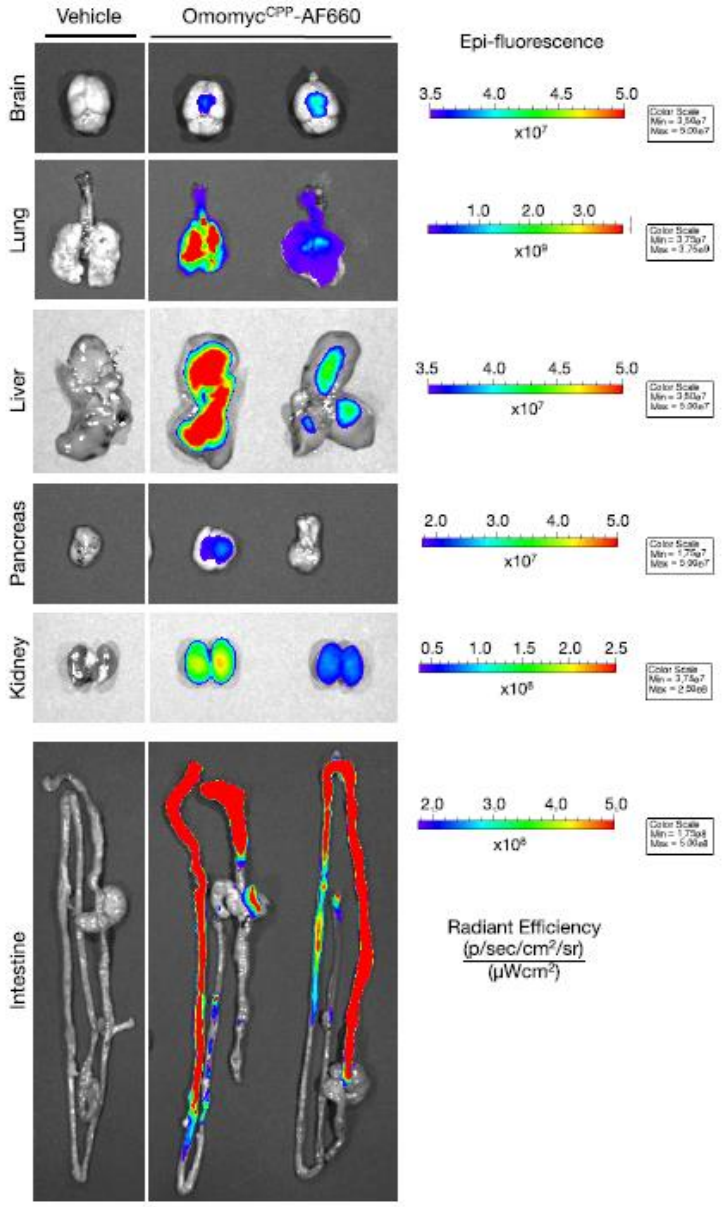
FIRST BIODISTRIBUTION STUDIES UPON I.N. ADMINISTRATION



Omomyc-AF660

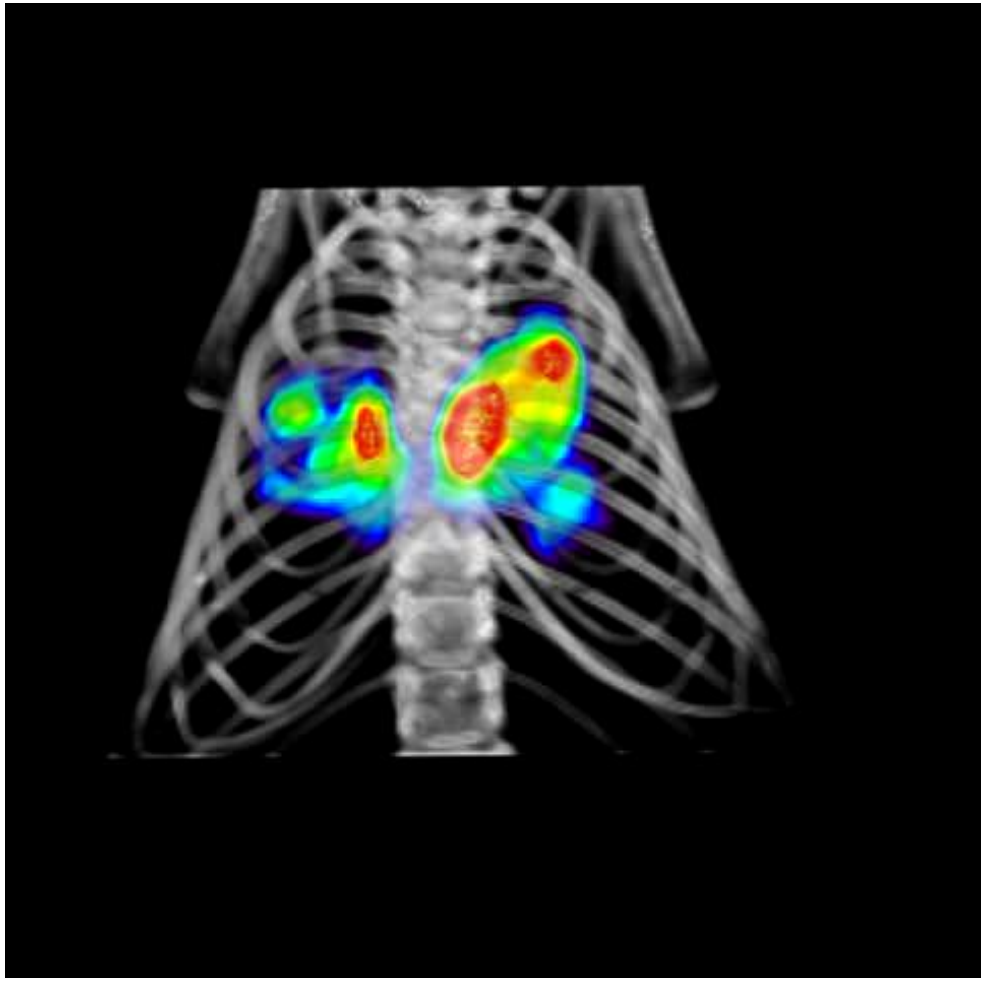


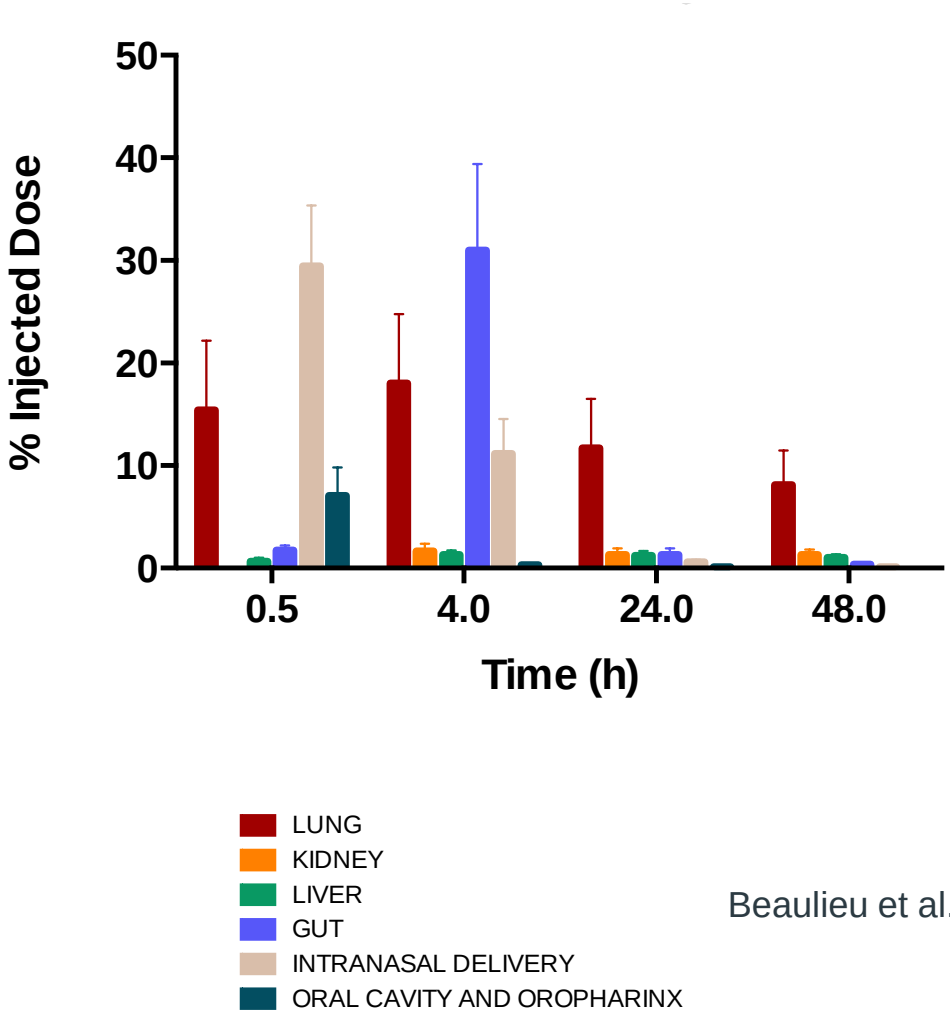
Lung



Beaulieu et al., 2019

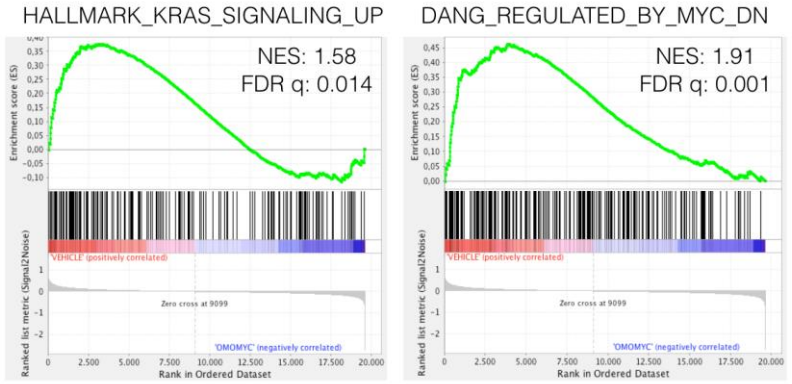
OMOMYC DISPLAYS TROPISM FOR TUMORS





Beaulieu et al., 2019

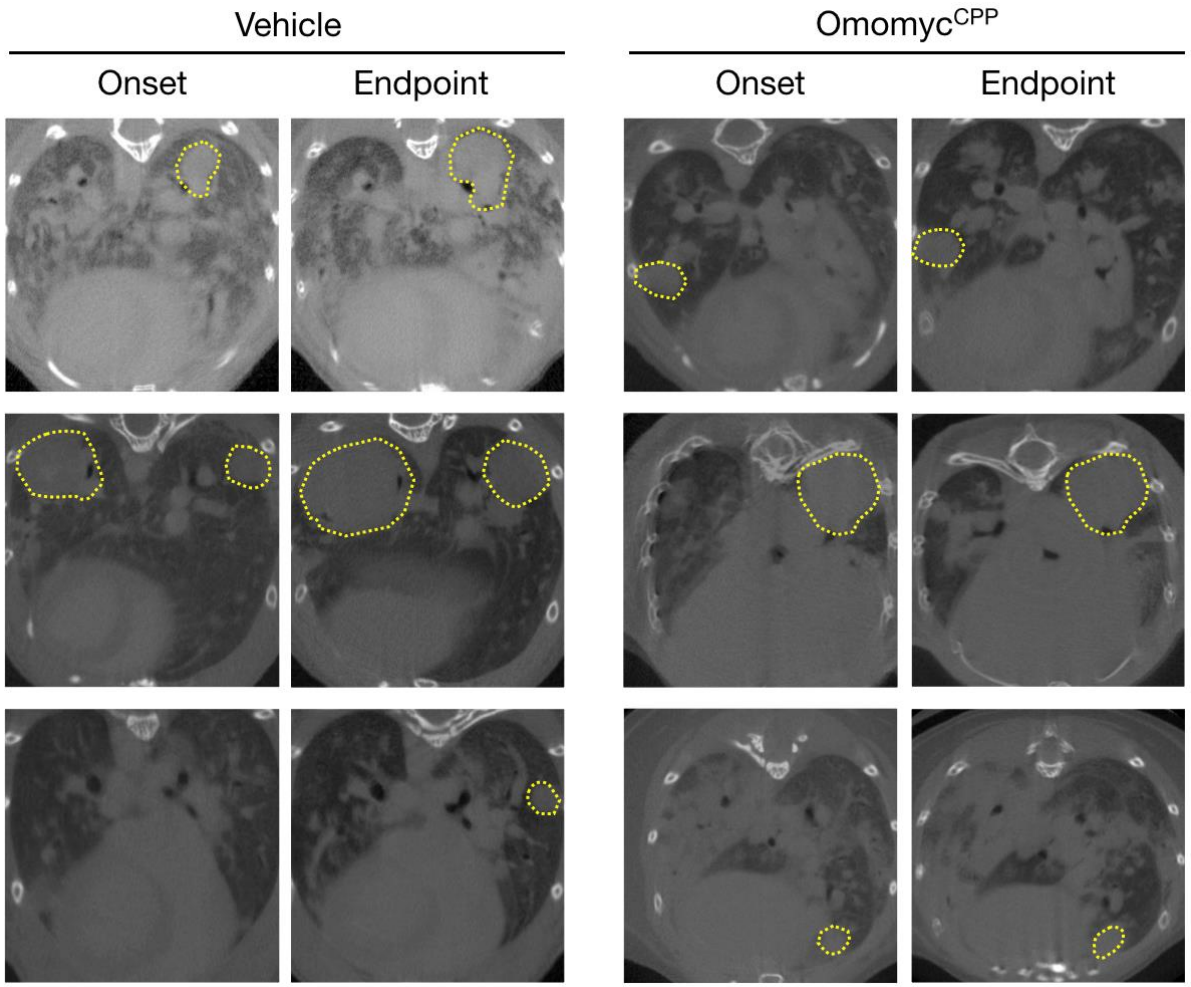
OMOMYC AFFECTS THE CROSS-TALK WITH THE TUMOR MICROENVIRONMENT

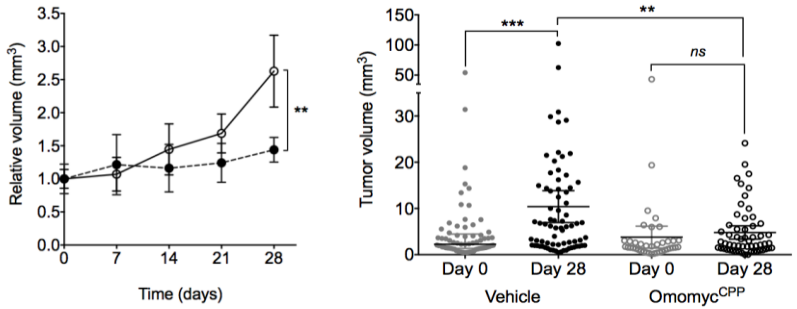


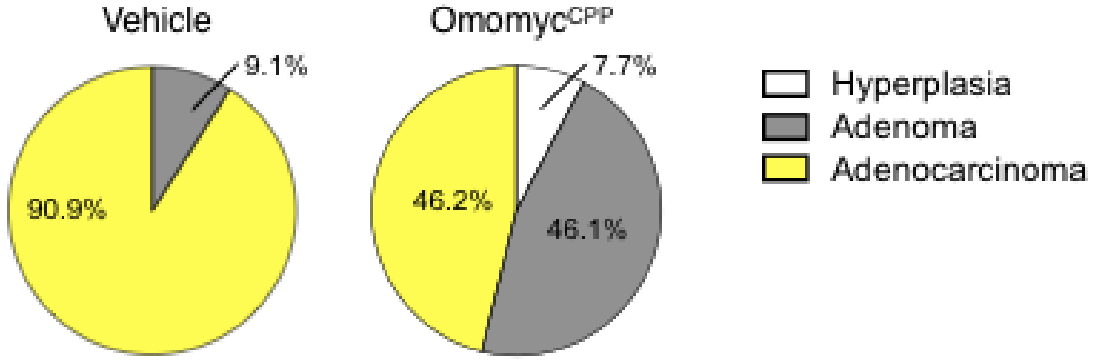
gene set	NES	FDR
DANG_MYC_TARGETS_DN	1.76	0.02
DANG_REGULATED_BY_MYC_DN	1.91	0.001
HALLMARK_KRAS_SIGNALING_UP	1.58	0.014
HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION	1.18	0.21
HALLMARK_HYPOXIA	1.55	0.019
KEGG_CHEMOKINE_SIGNALING_PATHWAY	1.99	0.0
KEGG_CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION	1.65	0.04
HALLMARK_PI3K_AKT_MTOR_SIGNALING	1.57	0.016
REACTOME_ERK_MAPK_TARGETS	1.62	0.111
REACTOME_MAPK_TARGETS_NUCLEAR_EVENTS_MEDIATED_BY_MAP_KINASES	1.55	0.144
HALLMARK_HEDGEHOG_SIGNALING	1.15	0.239

Beaulieu et al., 2019

OMOMYC REDUCES TUMOR GROWTH AND TUMOR GRADE (2,37 mg/Kg)

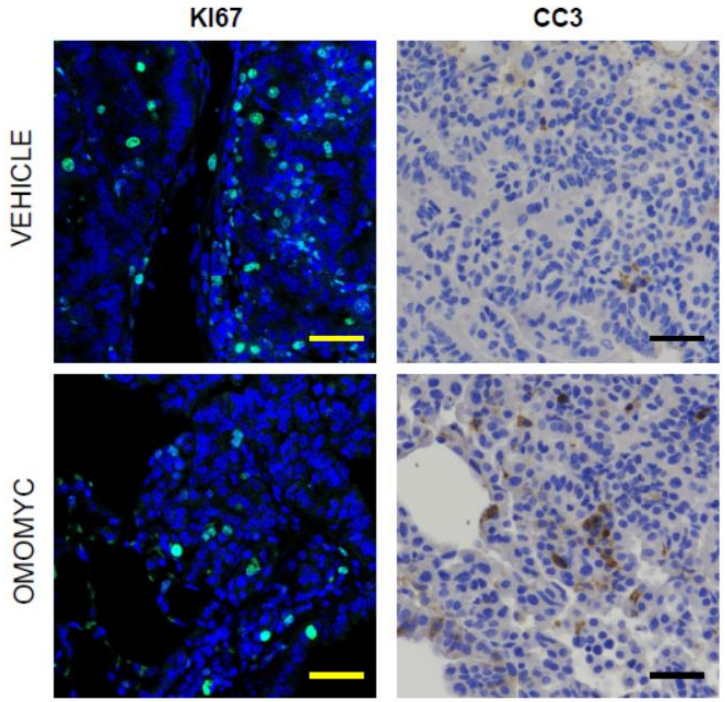


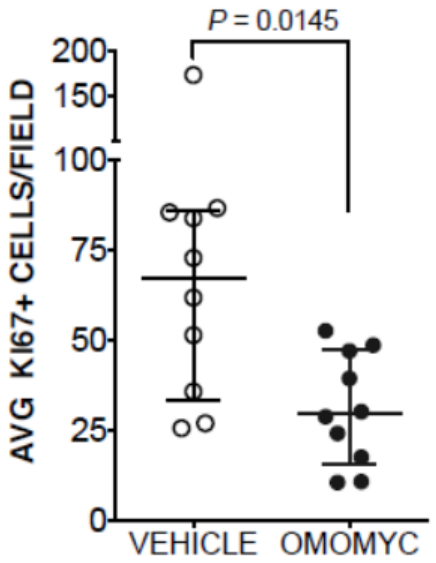


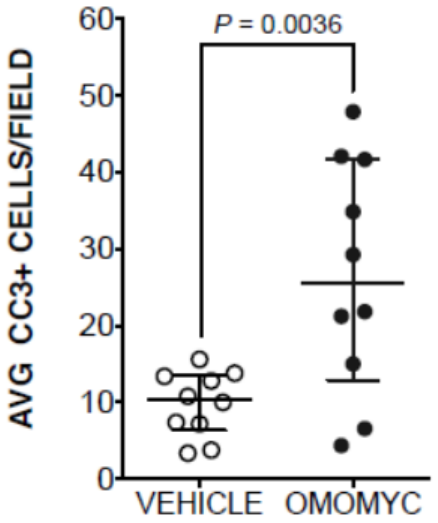


Beaulieu et al., 2019

OMOMYC REDUCES TUMOR PROLIFERATION AND INDUCES CELL DEATH

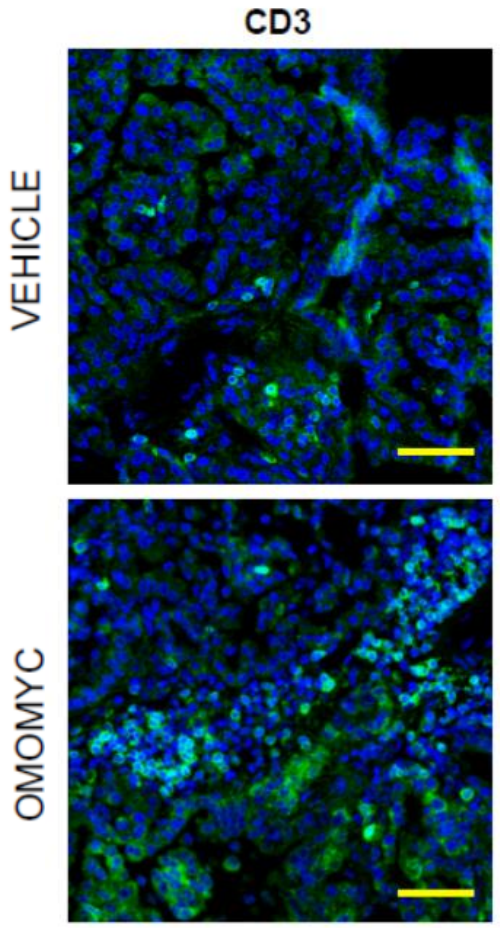




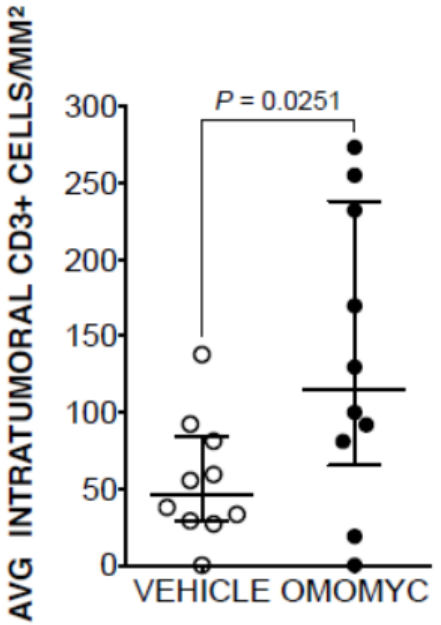


Beaulieu et al., 2019

OMOMYC PROMOTES INTRATUMORAL T-CELLS RECRUITMENT



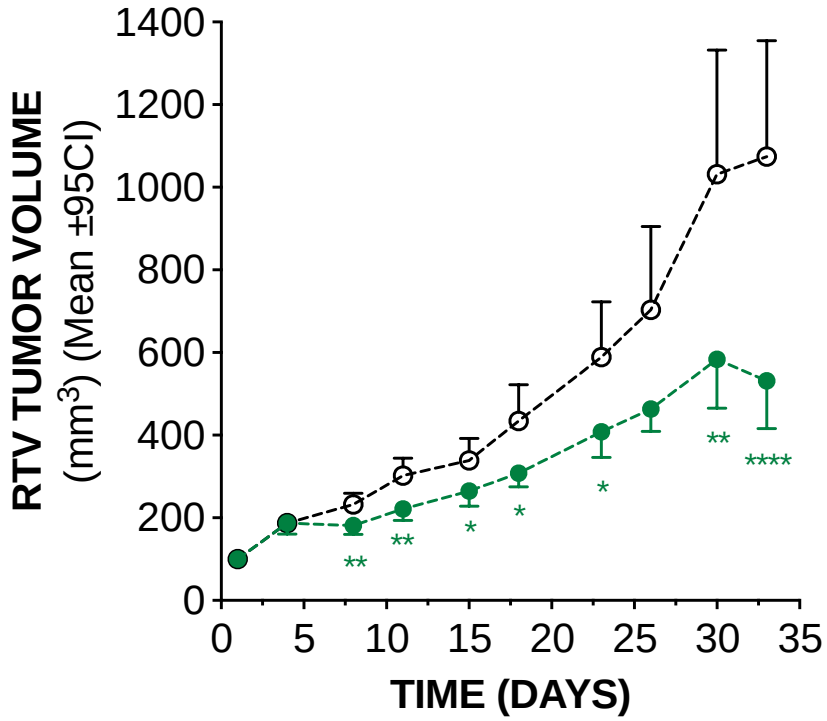
Potential for IO combination…

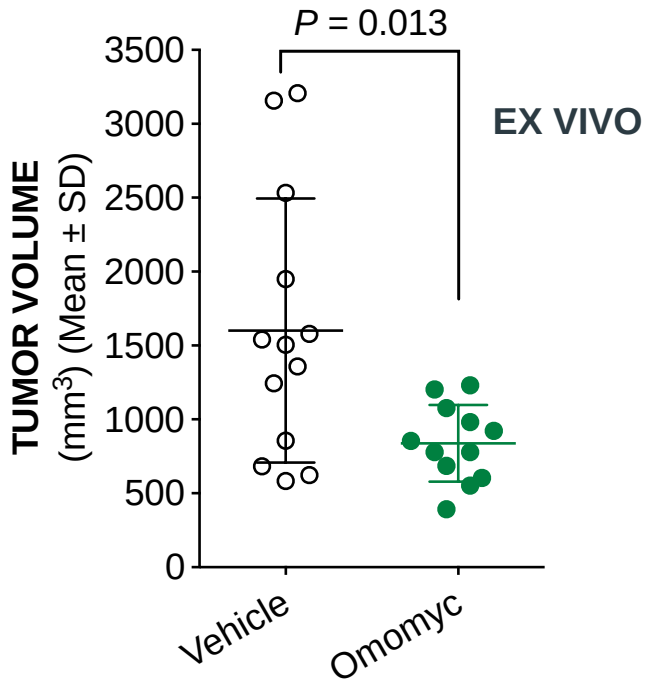


Beaulieu et al., 2019

EFFICACY OF I.V. ADMINISTRATION

SubQ implantation of H1975 (EGFR mutant, PI3K mutant, p53 mutant and resistant to Erlotinib)





Note: Omomyc displays a half-life of ~49 hours after i.v. administration

Beaulieu et al., 2019

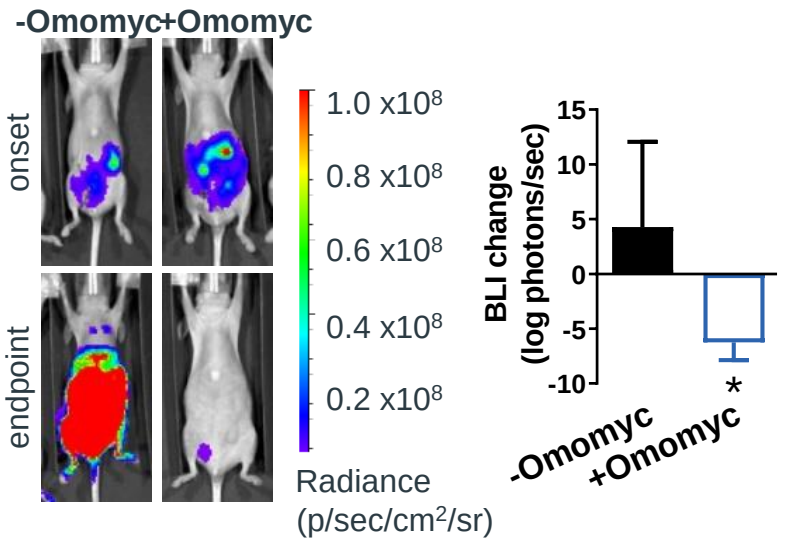
BEYOND NSCLC (OMOMYC IN TNBC METASTASES)

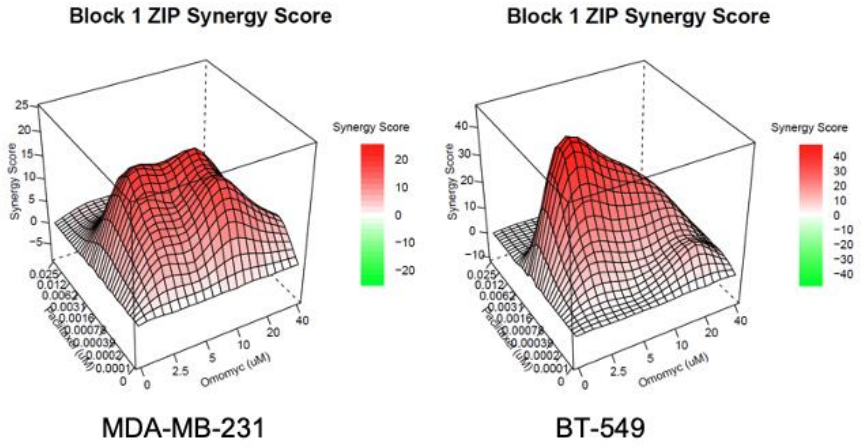
RESEARCH ARTICLE https://aacrjournals.org/10.1158/2767-9764.CRC-21-0103

MYC Inhibition Halts Metastatic Breast Cancer Progression by Blocking Growth, Invasion, and Seeding

Daniel Massó-Vallés[1,2,3], Marie-Eve Beaulieu[1,2], Toni Jauset[1,2,3], Fabio Giuntini[1], Mariano F. Zacarías-Fluck[1], Laia Foradada[2], Sandra Martínez-Martín[1,3], Erika Serrano[1], Génesis Martín-Fernández[1], Sílvia Casacuberta-Serra[2], Virginia Castillo Cano[2], Jastrinjan Kaur[1], Sergio López-Estévez[2], Miguel Ángel Morcillo[4], Mohammad Alzrigat[5], Loay Mahmoud[5], Antonio Luque-García[1], Marta Escorihuela[1], Marta Guzman[1], Joaquín Arribas[1,3,6], Violeta Serra[1], Lars-Gunnar Larsson[5], Jonathan R. Whitfield[1], and Laura Soucek[1,2,3,6]

(Massó-Vallés et al., Can Res Comm 2022)

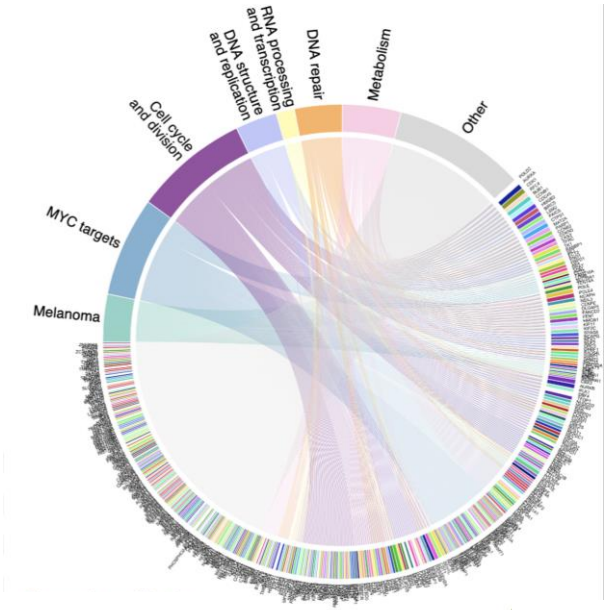


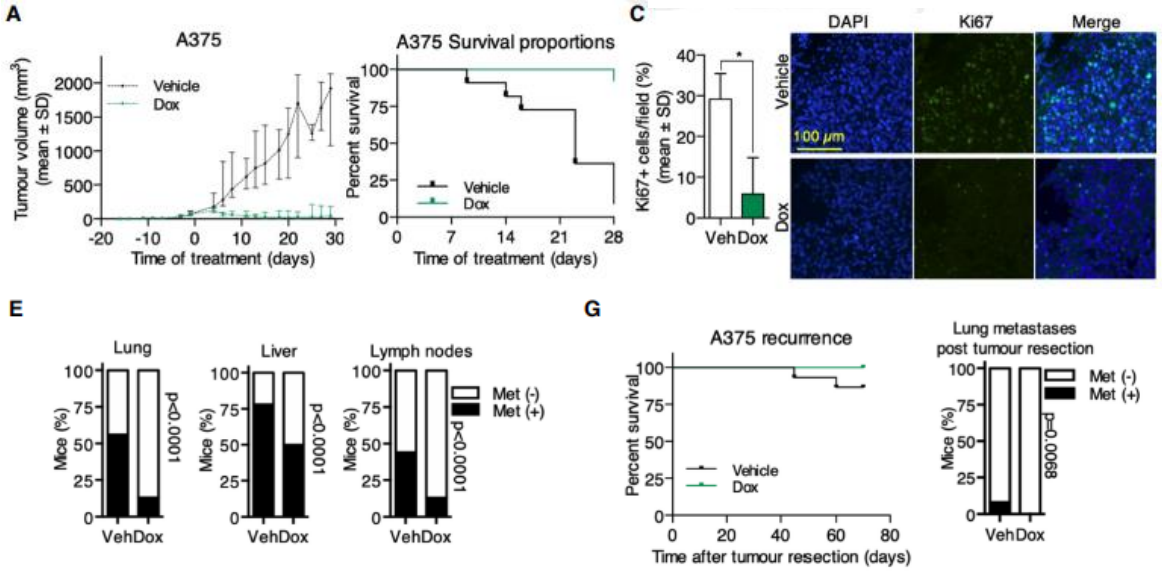


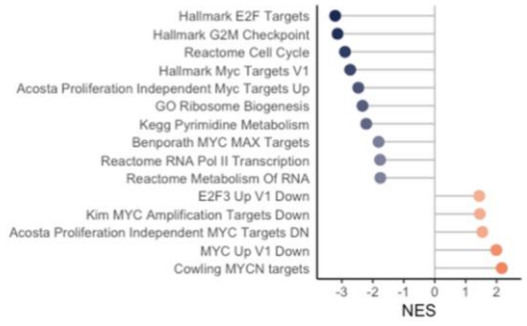
Reducing MYC's transcriptional footprint unveils a good prognostic gene signature in melanoma

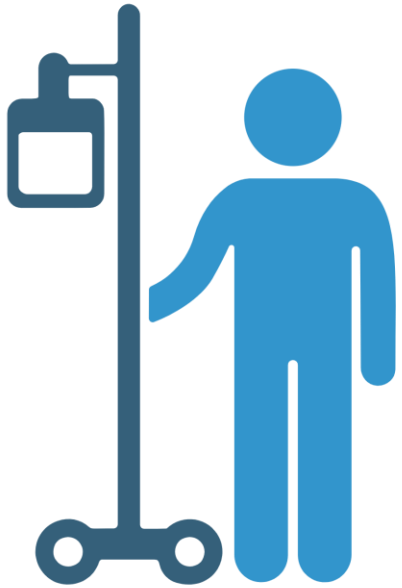
Mariano F. Zacarías-Fluck,[1] Daniel Massó-Vallés,[1,2,3] Fabio Giuntini,[1] Íñigo González-Larreategui,[1,4] Jastrinjan Kaur,[1] Sílvia Casacuberta-Serra,[1,2] Toni Jauset,[1,2,3] Sandra Martínez-Martín,[1,2,3] Génesis Martín-Fernández,[1,2] Erika Serrano del Pozo,[1] Laia Foradada,[2] Judit Grueso,[1,2] Lara Nonell,[5] Marie-Eve Beaulieu,[1,2] Jonathan R. Whitfield,[1] and Laura Soucek[1,2,3,6]

(Zacarias-Fluck et al.,Genes &Dev 2023)







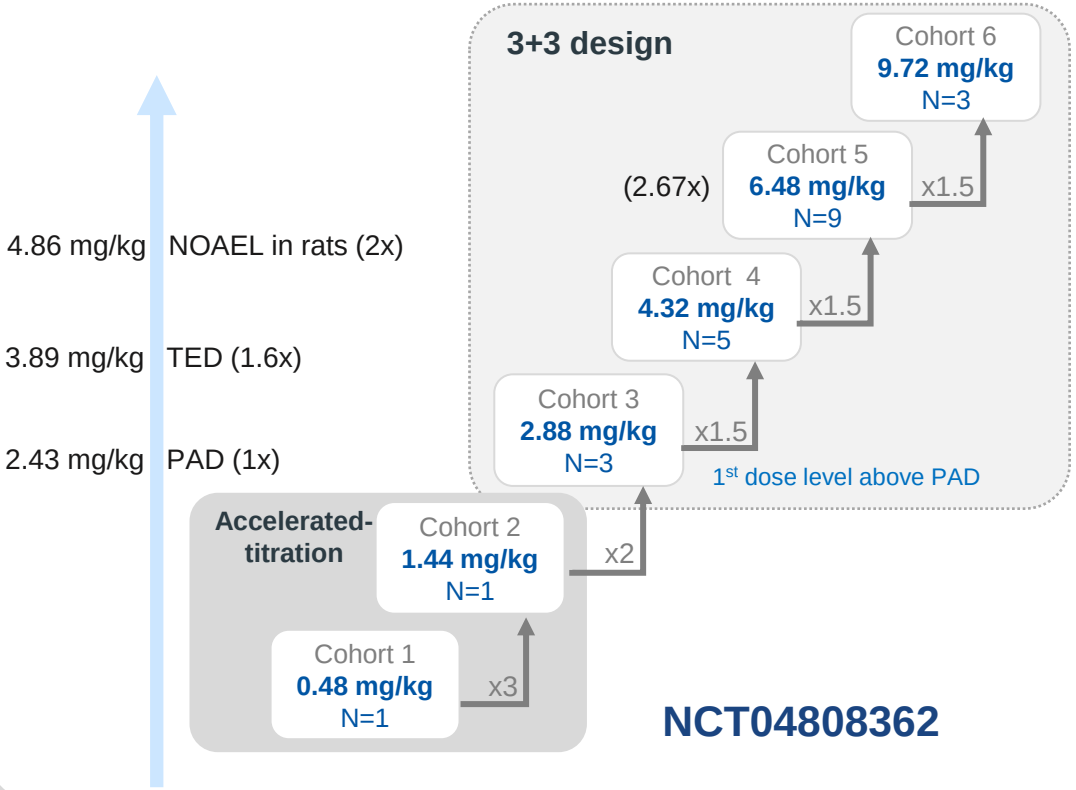


OMOMYC is the first direct MYC inhibitor to succesfully complete Phase I clinical trial in all comers solid tumors

Garralda et al., Nat Med 2024

Dose Escalation

- **1x weekly IV infusion (30'); 1 cycle = 3 weeks**
- **Primary endpoint:** Safety;
- **Secondary endpoints:** PK/PD, RP2D, preliminary efficacy and biomarkers



Garralda et al., 2024

22 patients included, all heavily pre-treated (2-12 previous lines)

- 19 evaluable patients

Excellent safety:
Mainly grade 1 events

Efficacy:
Long-lasting Stable Diseases in 8 out of 12 patients (by RECIST, first CT scan after 3 cycles (9 weeks), and every 3 cycles after that) and **one PR by total tumor burden volumetric analysis**

RP2D= DL5, based on PK, AEs (IRRs), and **target engagement**

Garralda et al., Nat Med 2024

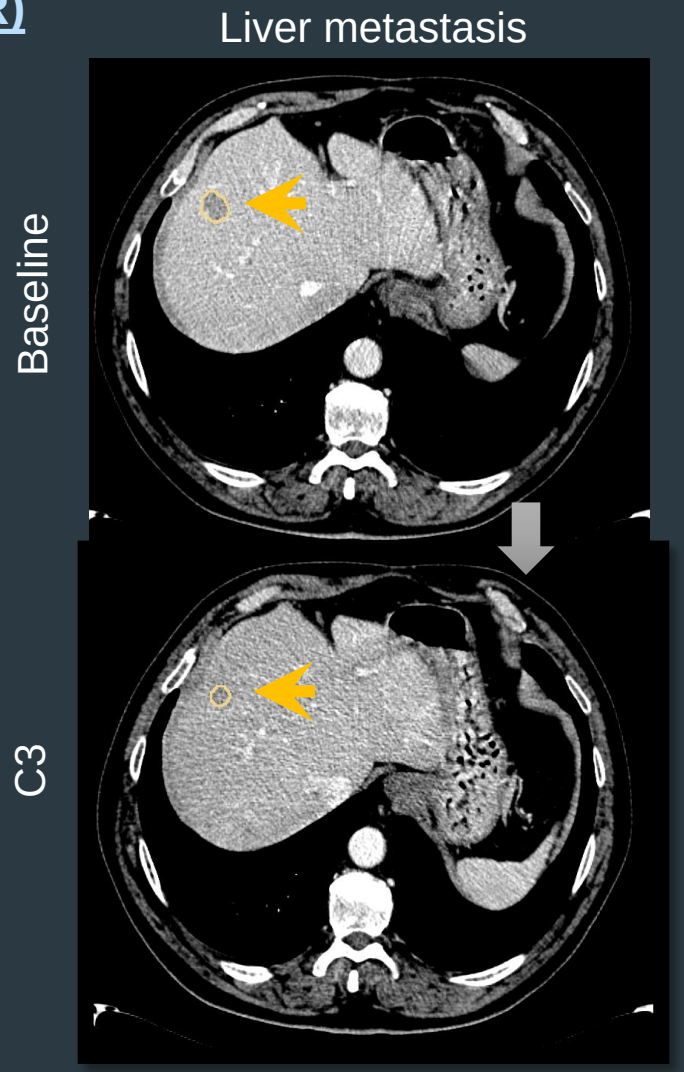
PARTIAL RESPONSE CASE

Volumetric analysis of total tumor burden reveals **one partial response (PR)**

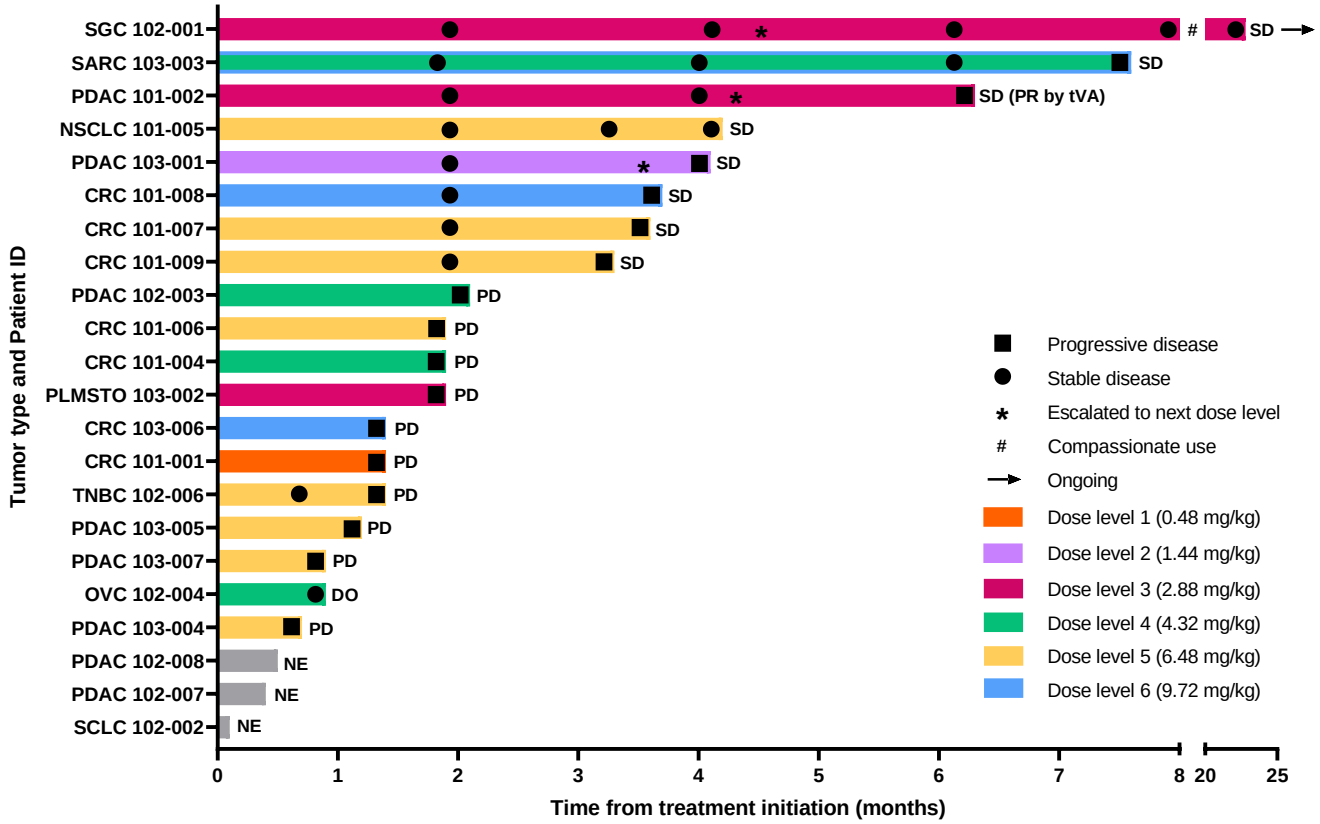
- 73 y, male patient in DL3. ECOG 0
- PDAC with liver mets. 3 prior treatment lines
- CT scan after 3 and 6 cycles : SD
- Remained in study 7 months

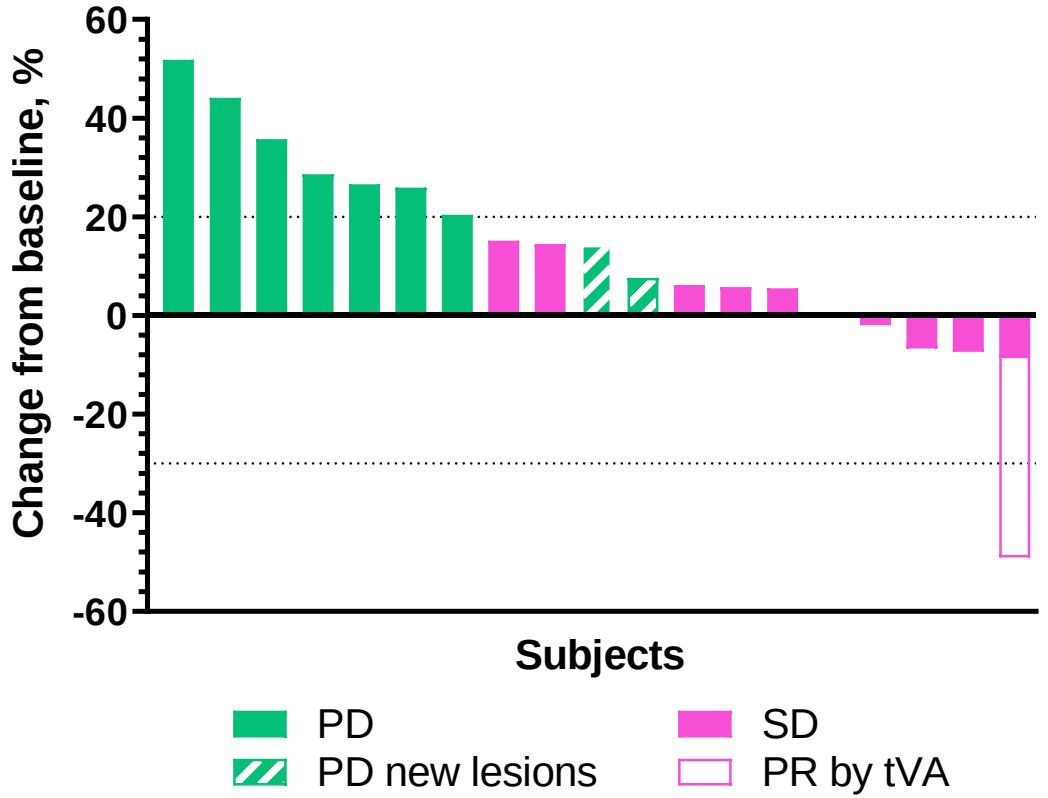
Patient 101-002 achieved an overall **49% reduction of total tumour burden** at best response, when evaluating the sum of volume of all lesions.

Garralda et al., Nat Med 2024



OMOMYC IN CLINICAL TRIALS





Garralda et al., Nat Med 2024

PK DATA (PRECLINICAL CLINICAL)

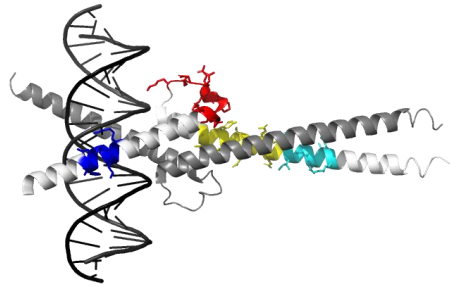
cancers

MDPI

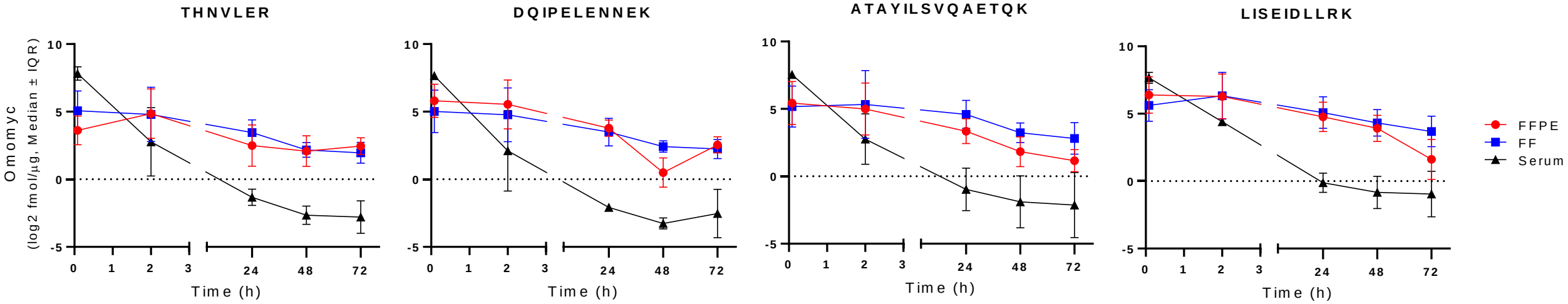
Communication

Pharmacokinetic Analysis of Omomyc Shows Lasting Structural Integrity and Long Terminal Half-Life in Tumor Tissue

Marie-Eve Beaulieu [1,*,†], Sandra Martínez-Martín [1,†], Jastrinjan Kaur [2], Virginia Castillo Cano [1], Daniel Massó-Vallés [1], Laia Foradada Felip [1], Sergio López-Estévez [1], Erika Serrano del Pozo [2], Hugo Thabussot [1] and Laura Soucek [1,2,3,4,*]

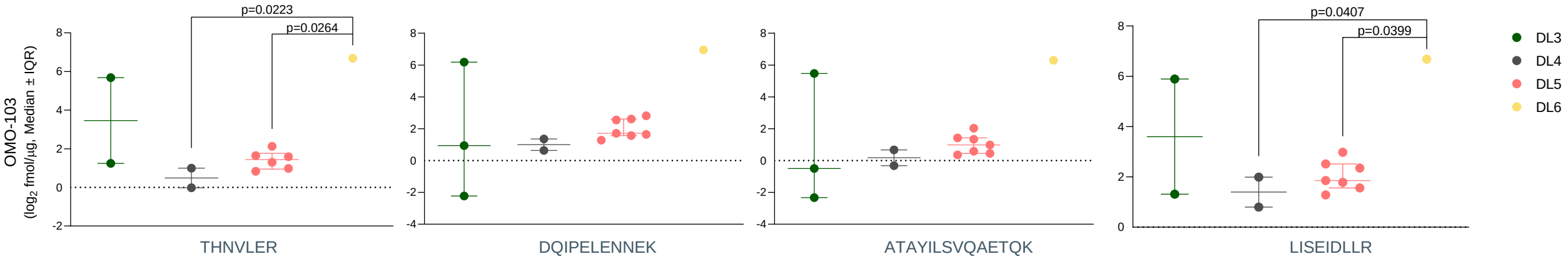


Nt-TEENVKRRTHNVLERQRRNELKRSFFALRDQIPELENNEKAPKVVILKKATAYILSVQAETQKLISEIDLLRKQNEQLKHKLEQLRNSCA-Ct



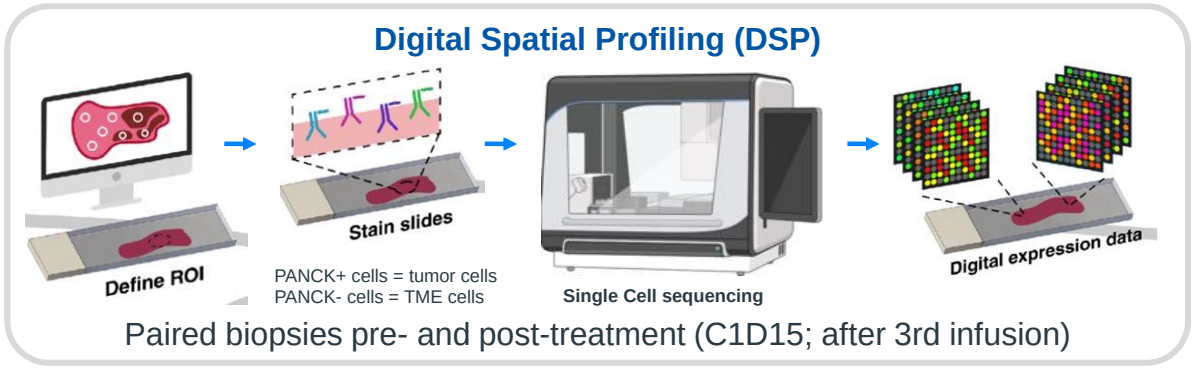
PK: terminal half-life in serum >40h (dose levels 3-6)

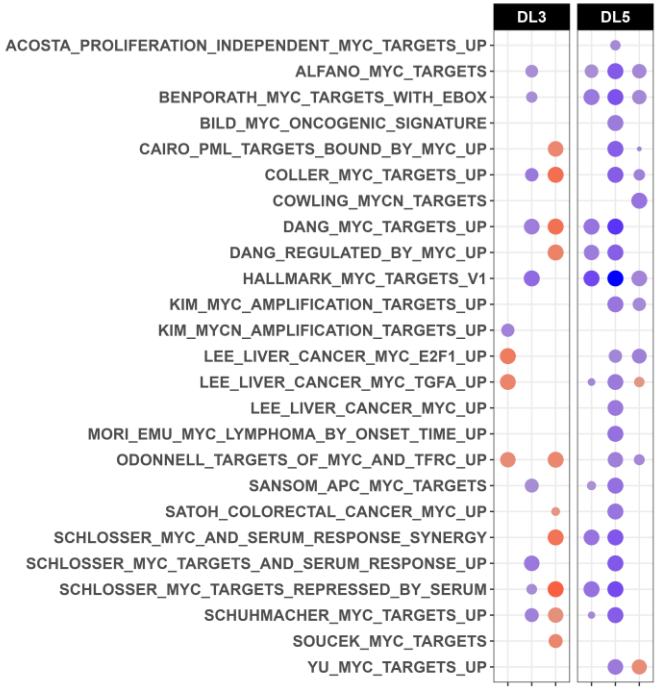
- Likely underestimated as samples were collected up to 96h post-treatment
- **Intact OMO-103** detected **in patient tumor biopsies** by mass spectrometry **up to 19 days after last infusion**

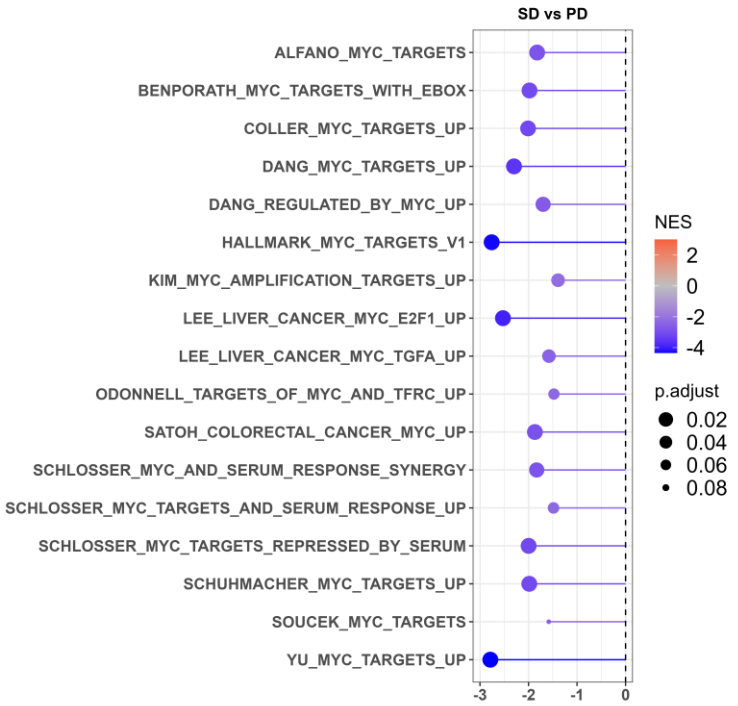


Garralda et al., Nat Me

PROOF OF TARGET ENGAGEMENT

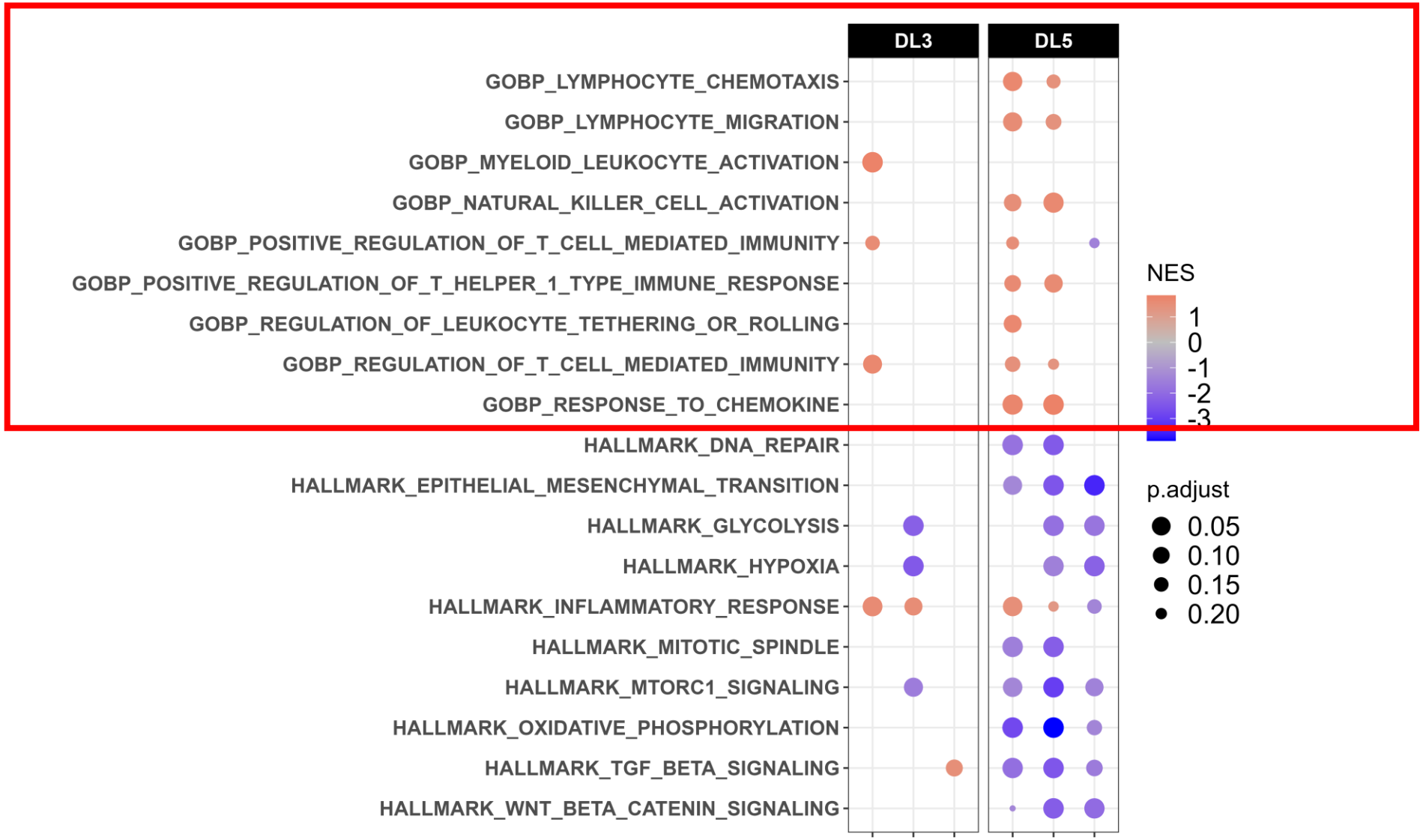






Garralda et al., Nat Med 2024

TARGET ENGAGEMENT IMPACT ON IMMUNE RESPONSE

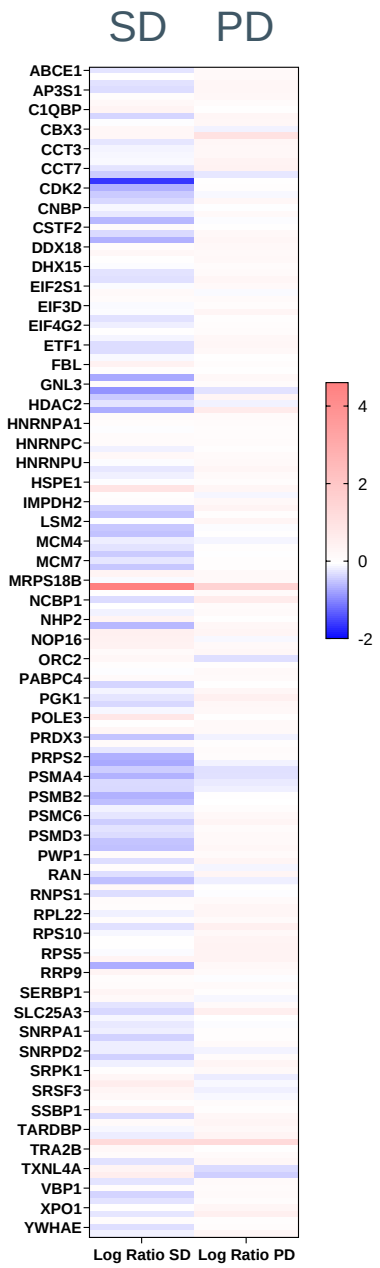


Garralda et al., Nat Med 2024

ULTRADEEP PROTEIN PROFILING CONFIRMS BETTER TARGET ENGAGEMENT ASSOCIATED TO CLINICAL BENEFIT

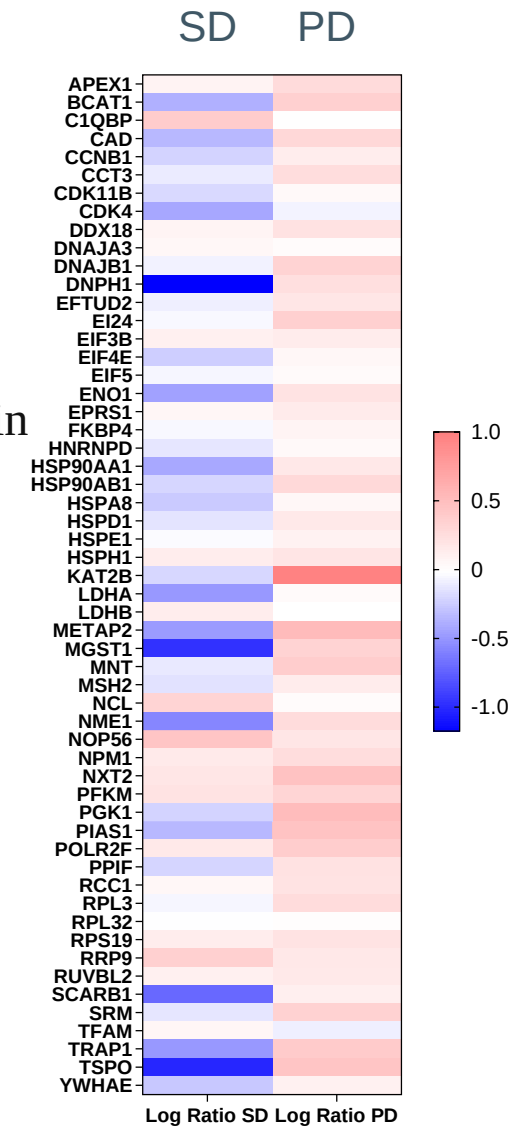
MYC Hallmark_v1

110/179 proteins downregulated in SD patients;
35/179 in PD patients.



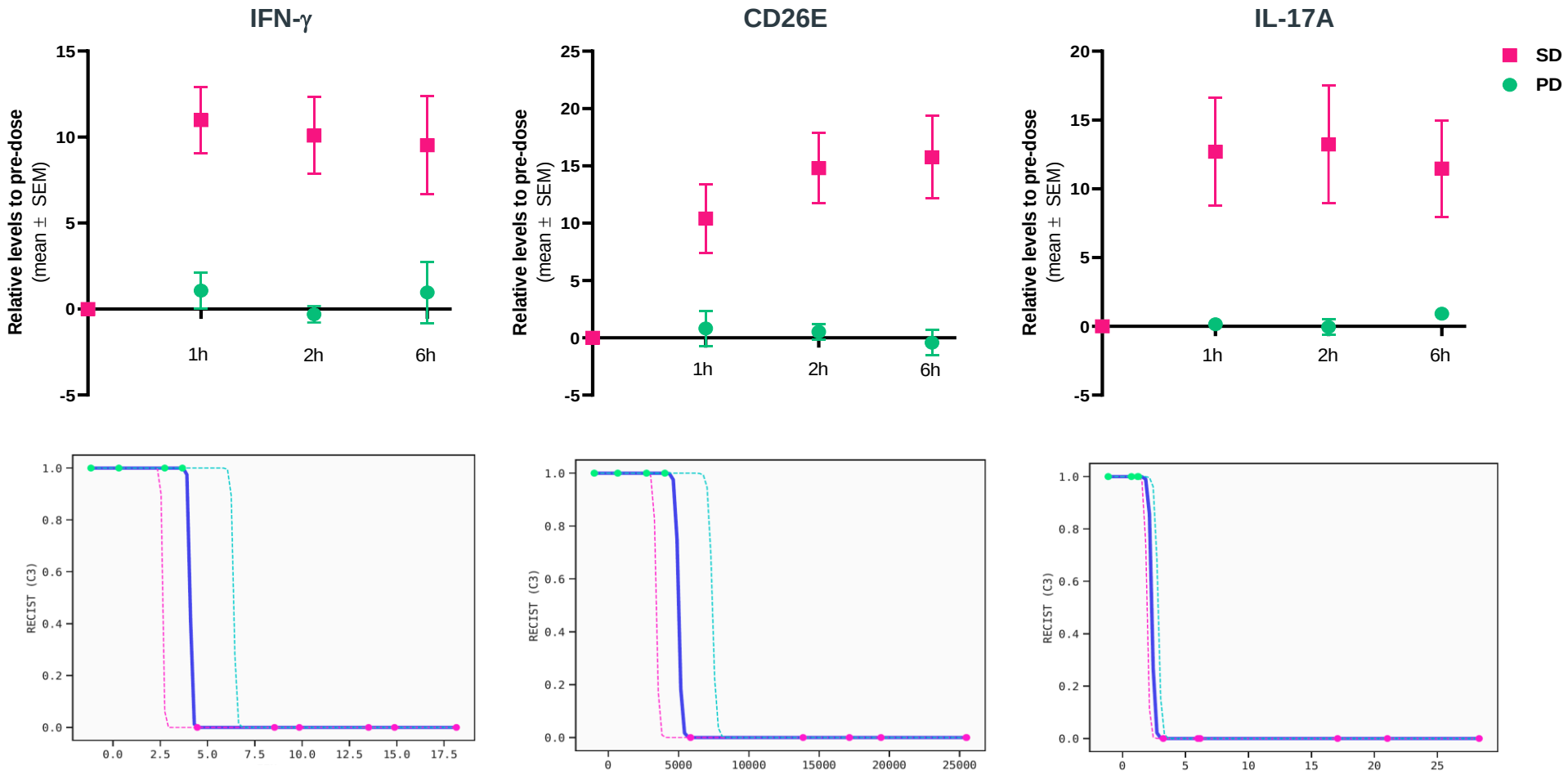
MYC targets

37/56 proteins downregulated in SD patients;
3/56 in PD patients.



Garralda et al.,Nat Med 2024

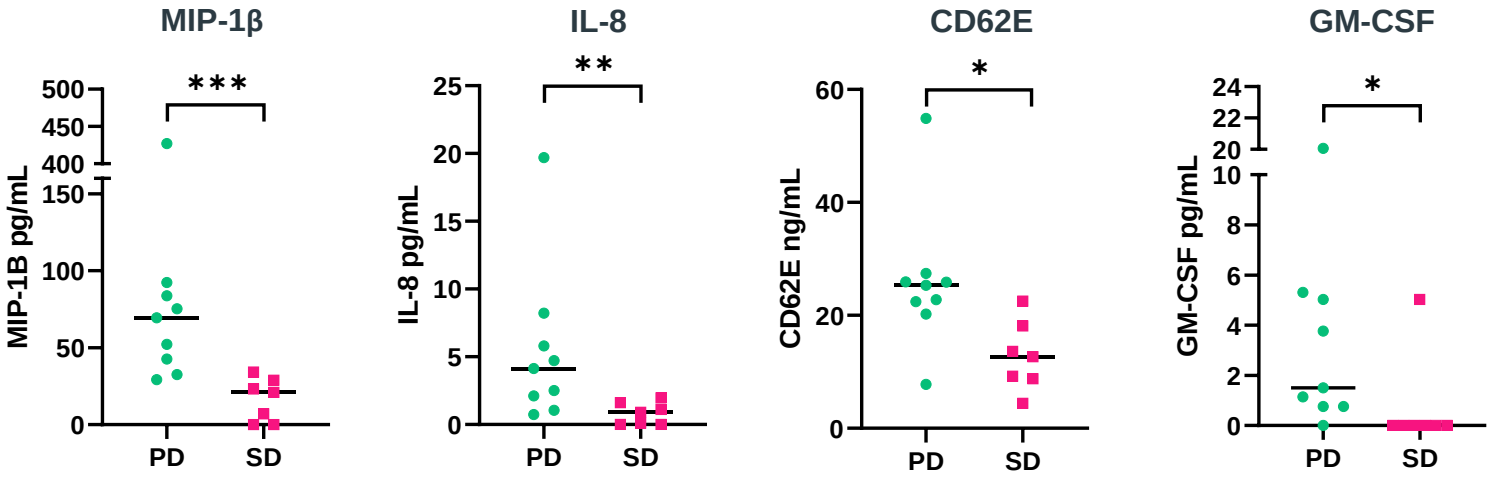
IDENTIFIED LIQUID PD BIOMARKERS

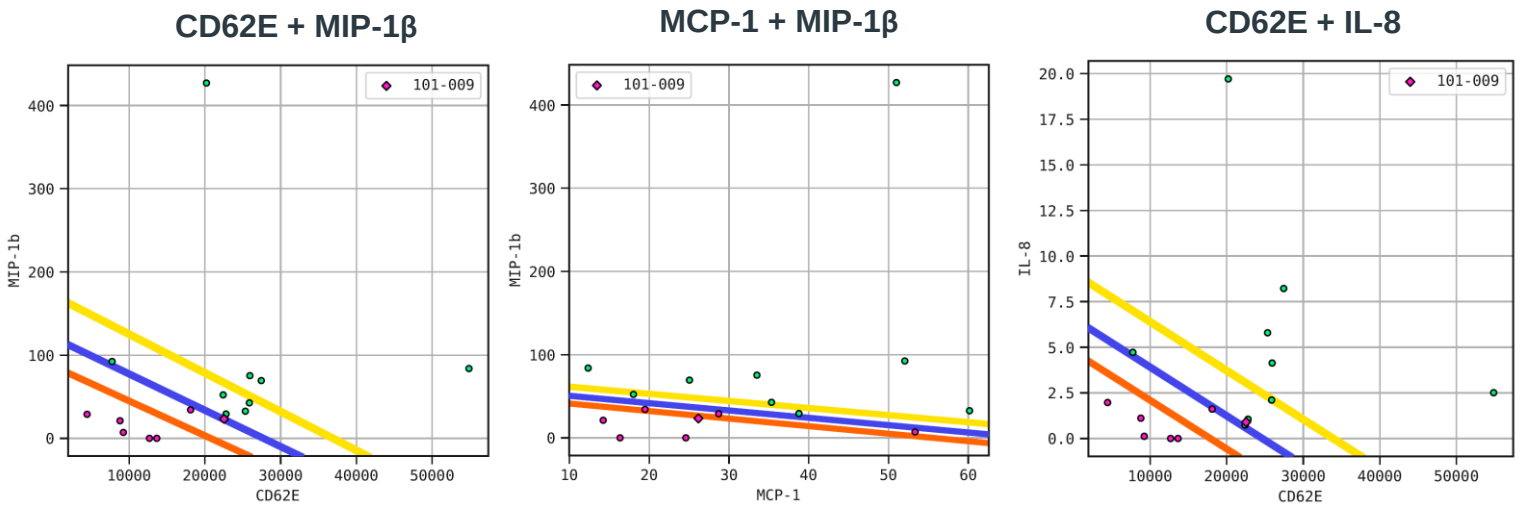


Signature identified at Peptomyc and independently confirmed by Abzu

Garralda et al., Nat Med 2024

POTENTIAL PREDICTIVE BIOMARKERS





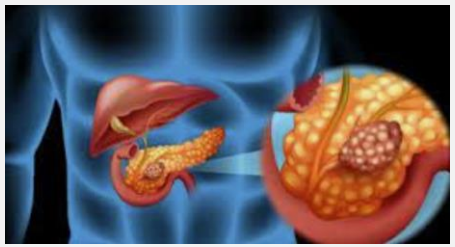
Signature identified at Peptomyc and independently confirmed by Abzu

Garralda et al., Nat Med 2024

ONGOING: PHASE Ib

Safety run-in followed by Expansion Phase

- **Primary endpoint:** Safety
- **Secondary endpoints:** Efficacy, PK/PD, and biomarkers
- Use of the identified predictive biomarkers as selection criteria



3+3 design

DL 5
6.5 mg/kg
N=12-15

x1.5

DL 4
4.3 mg/kg
N=3-6

Gemcitabine/Nab-paclitaxel (PDAC, 1st line) + OMO-103

10 months treatment duration

JUST STARTED: PHASE II

Phase 2 proof-of-concept study of OMO-103 in high-grade Osteosarcoma

- **Primary endpoint:** Efficacy (PFS at 16 weeks)
- **Secondary endpoints:** Safety, PK/PD, Biomarkers and QoL

DL 5

6.5 mg/kg as weekly infusion

N=10

treatment until progression, 12m OS follow-up

COMING SOON: WINDOW OF OPPORTUNITY TRIAL

Monotherapy (IND 173879)

phase 1 trial to assess the pharmacodynamics of OMO-103 in participants with PDAC

- preliminary estimate of measurable changes in tumor biology among participants before (i.e., baseline) and after receiving OMO-103

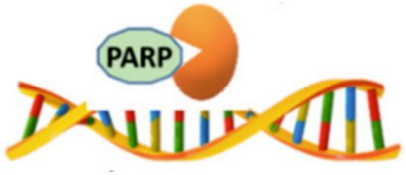
DL 5
6.5 mg/kg
N=10-12

infusion of OMO-103 on Days 1 and 8 of a 10-day treatment period; 1 year follow-up.

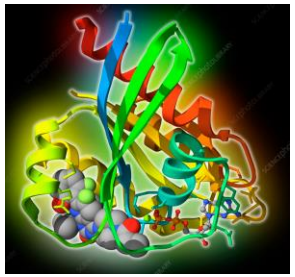
IN PARALLEL: BACK TO THE LAB AND TO (MANY) OPEN QUESTIONS

Brain delivery?

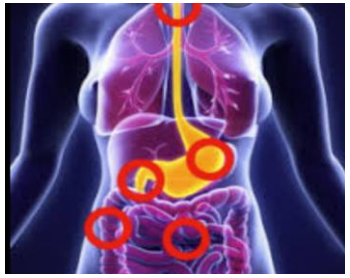
MYC role in DDR?



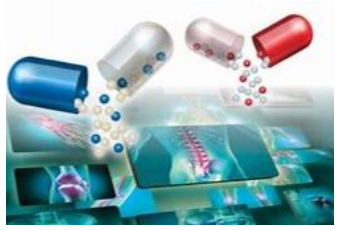
Oncogene cooperation?



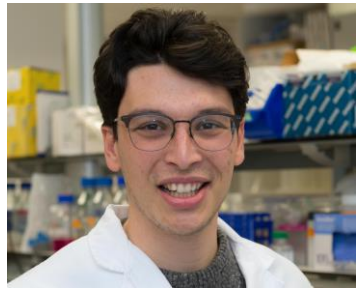
Max null tumors?

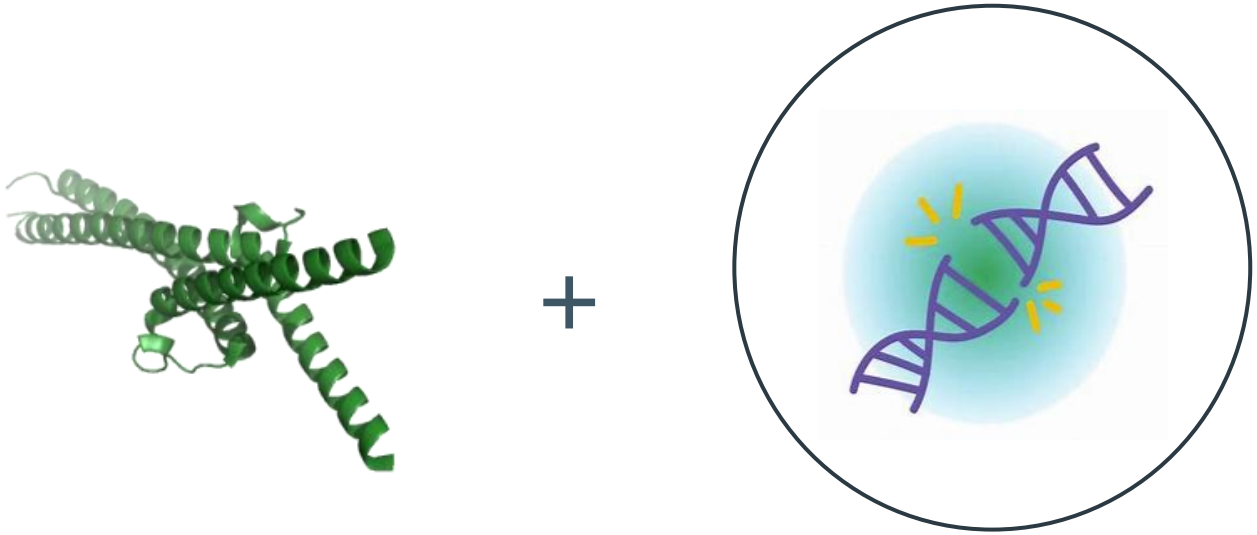


Best therapeutic combination?



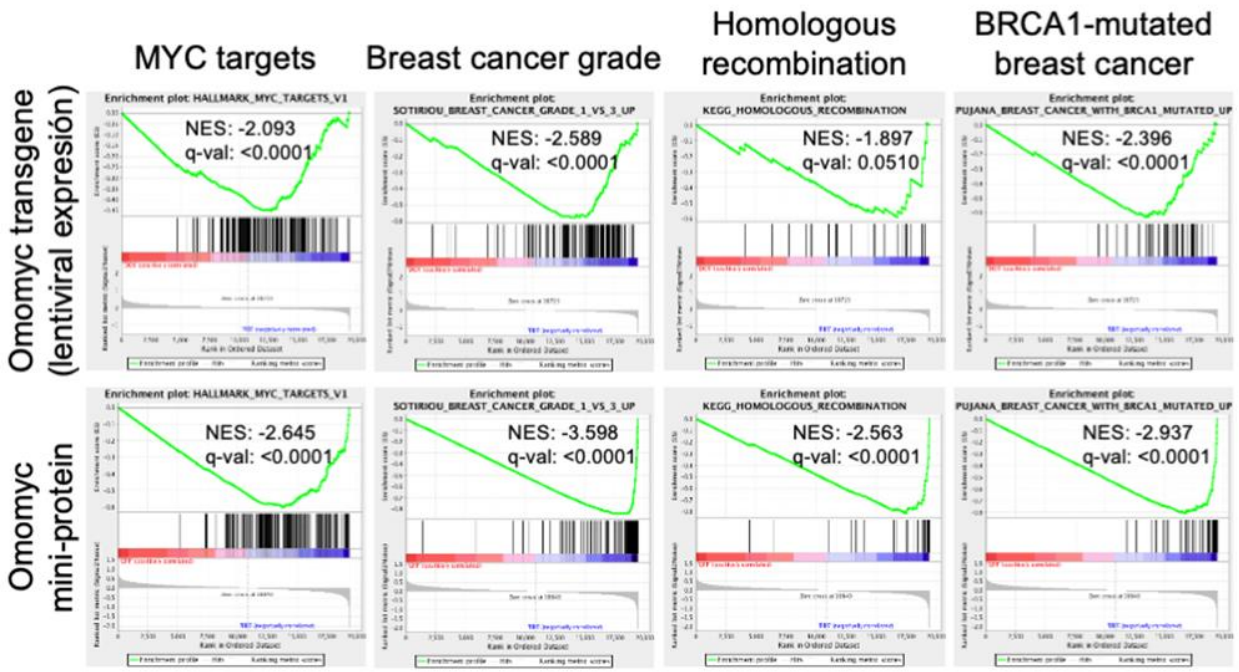
MYC AND DNA DAMAGE

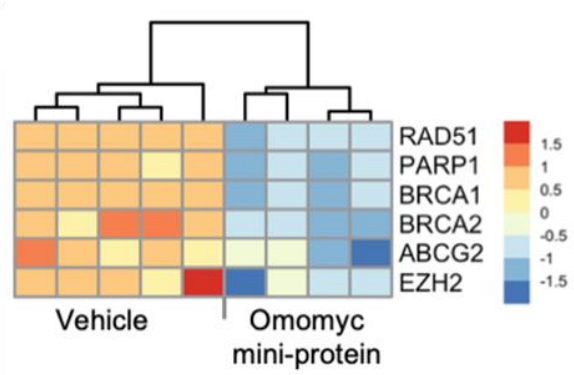




FIRST OBSERVATION: OMOMYC NEGATIVELY REGULATES DDR IN TNBC MODELS

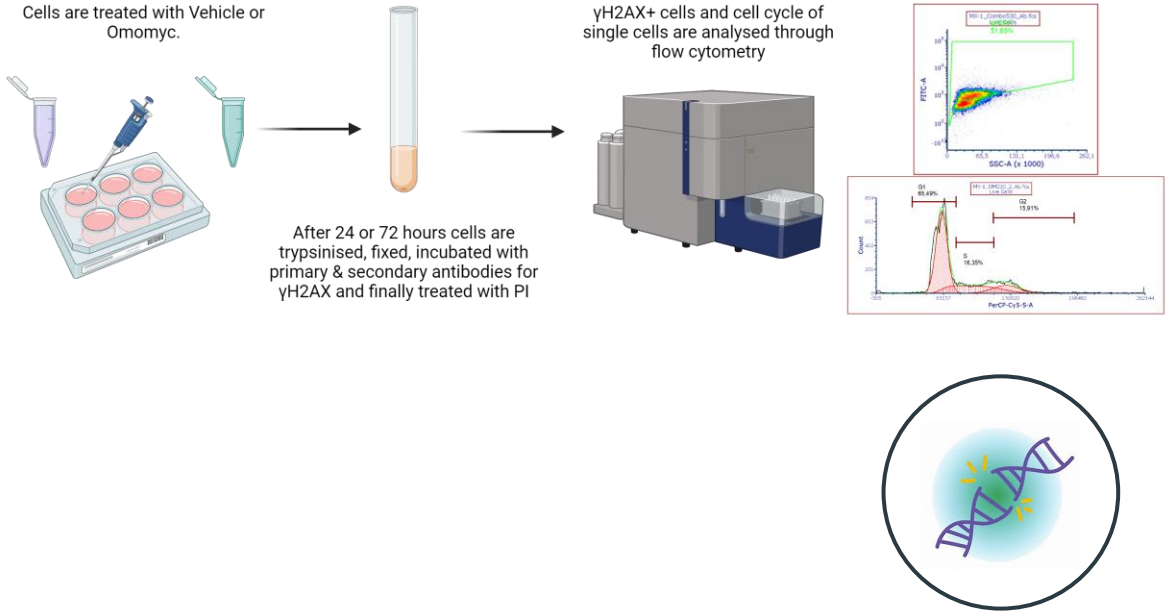
In MDA-MB-231 a benchmark cell line for BRCA wildtype TNBC:

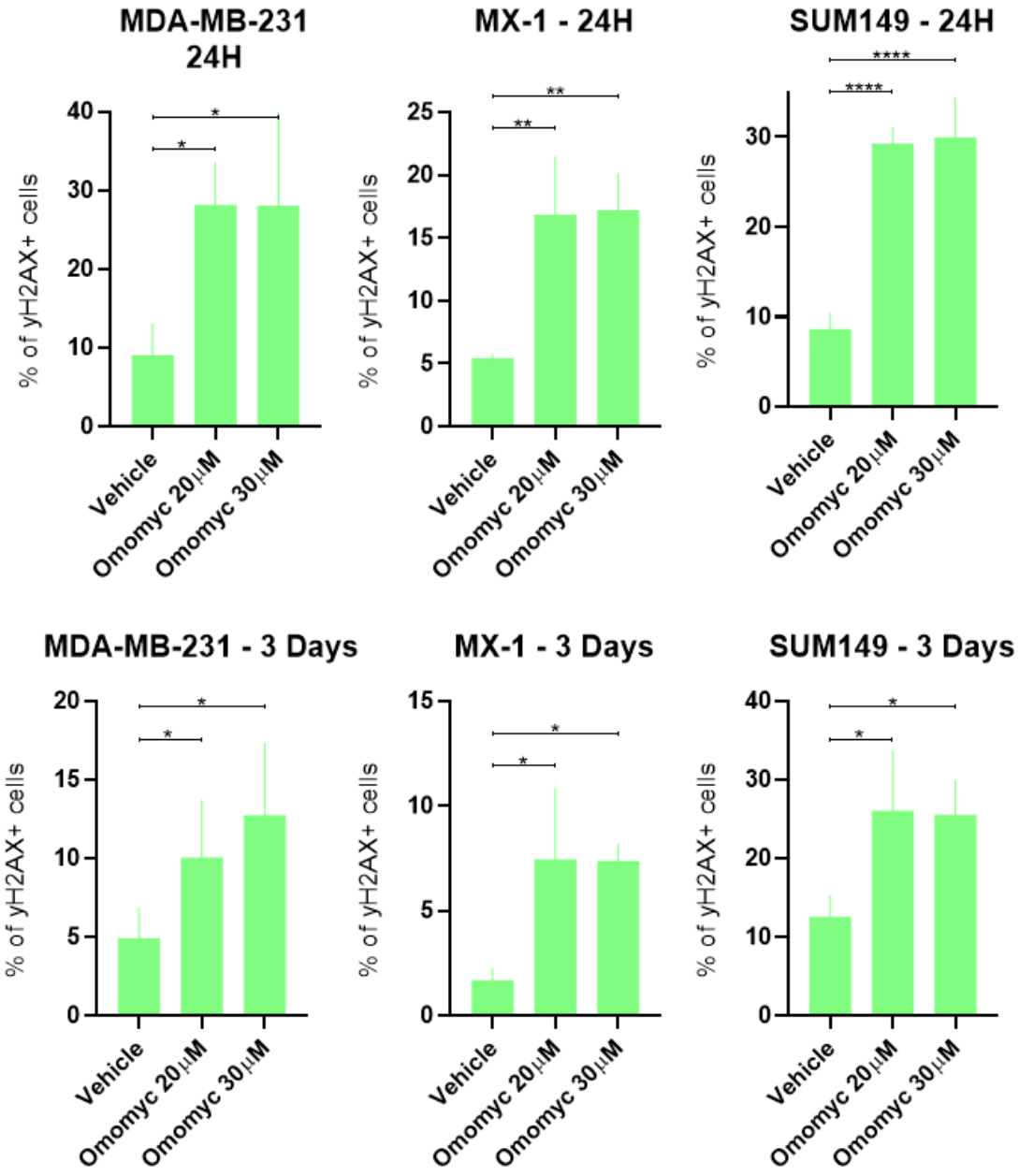




OMOMYC induces defects in DNA Damage Repair
(very similar to BRCA mutation and PARP inhibition at once)

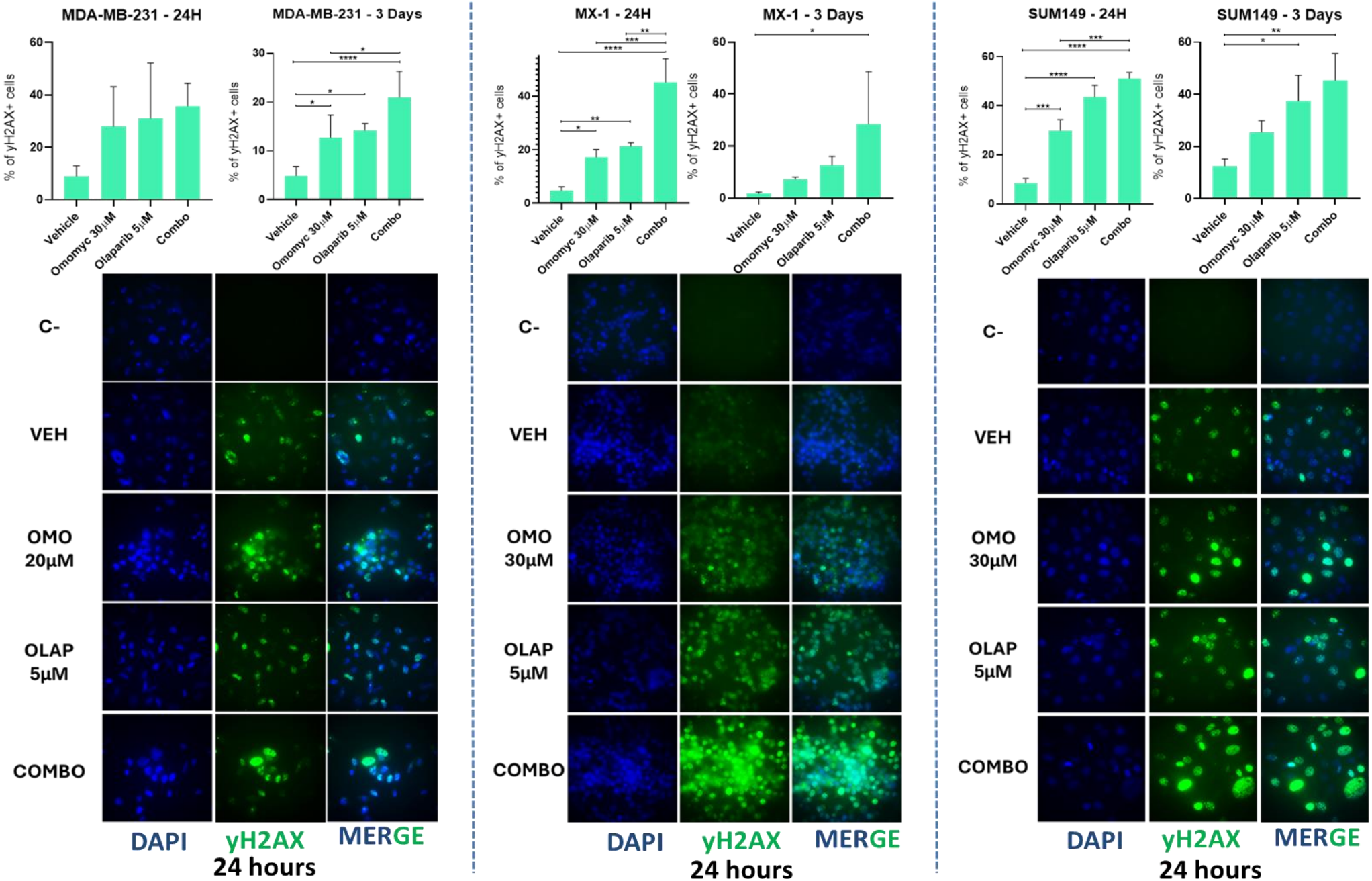
OMOMYC INDUCES DNA DAMAGE (γH2AX)





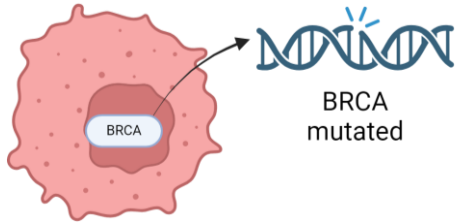
Unpublished data

OMOMYC CONTRIBUTES TO INCREASING DNA DAMAGE IN THE PRESENCE OF PARPi



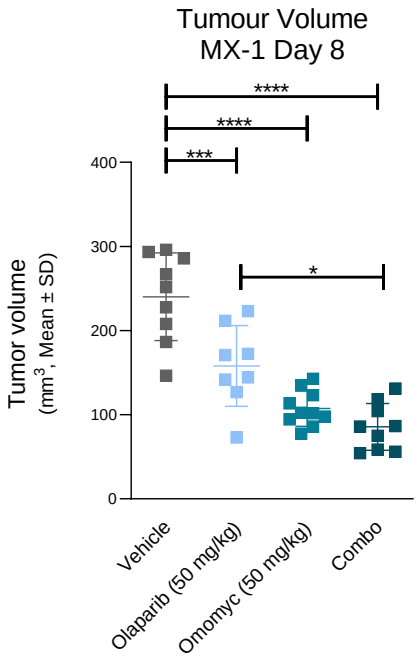
Unpublished data

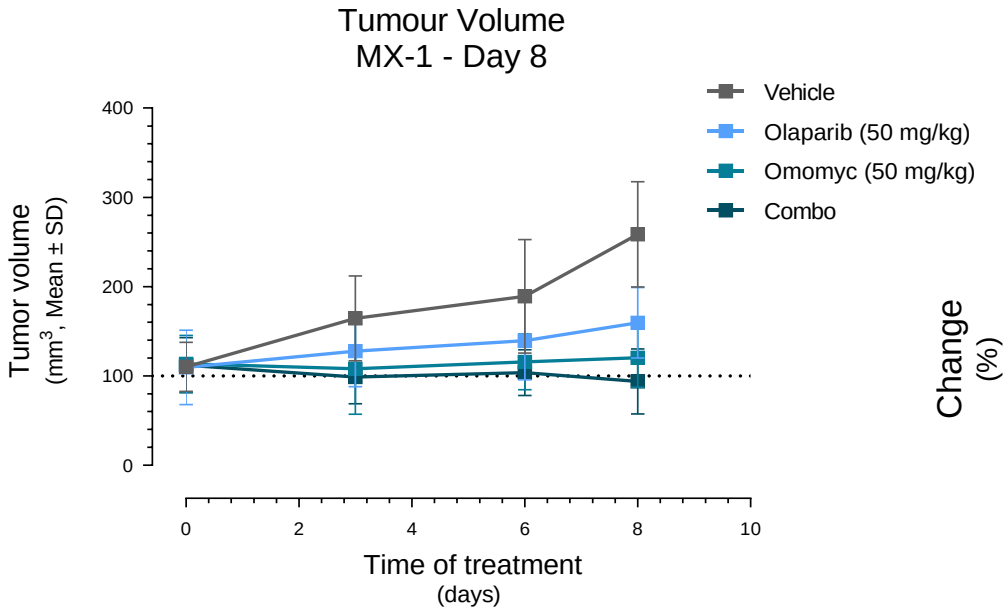
OMOMYC REVERTS OLAPARIB RESISTANCE IN VIVO

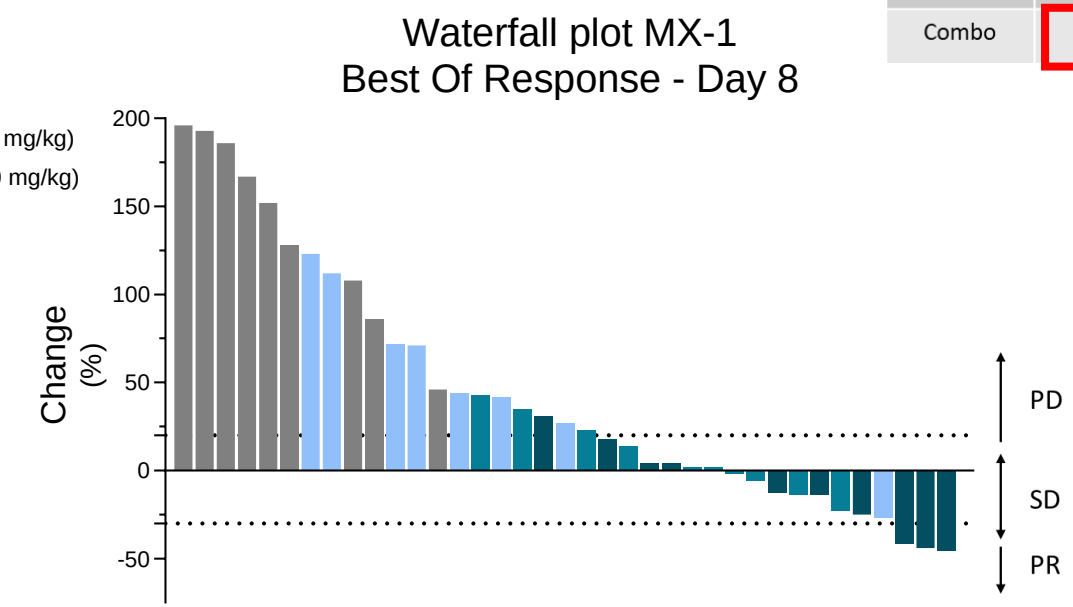


MX-1: Partially Resistant to PARPi

Treatment	DCR
Vehicle	0%
Olaparib	13%
Omomyc	70%
Combo	90%

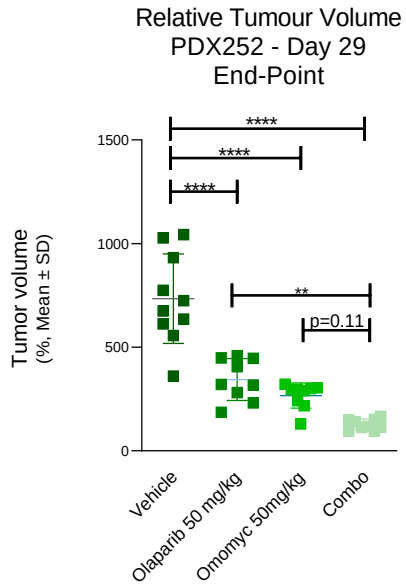


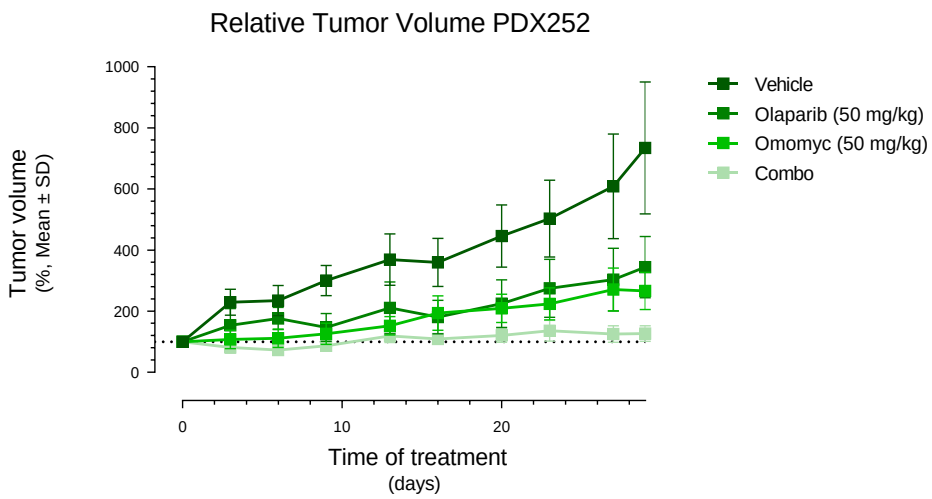




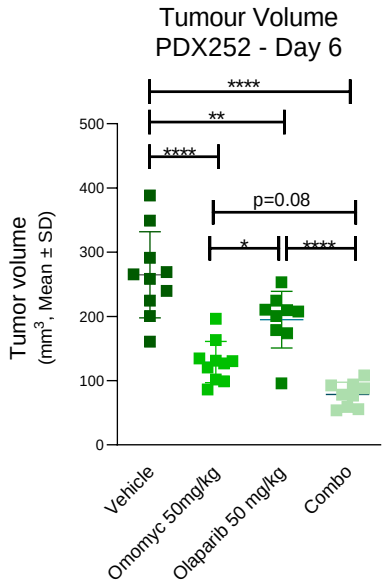
Unpublished data

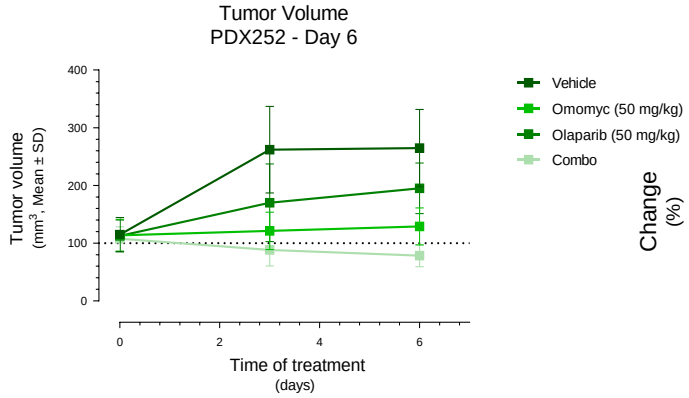
OMOMYC CAN SENSITIZE OLAPARIB RESISTANT PDXs TO PARPi

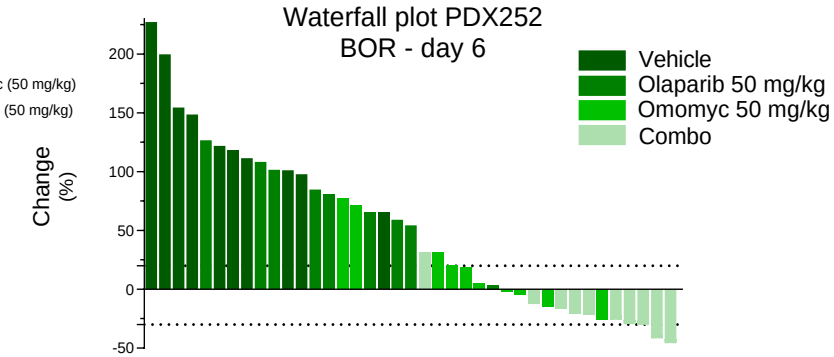




Treatment	DCR
Vehicle	0%
Olaparib	11.1%
Omomyc	60%
Combo	90%







Unpublished data

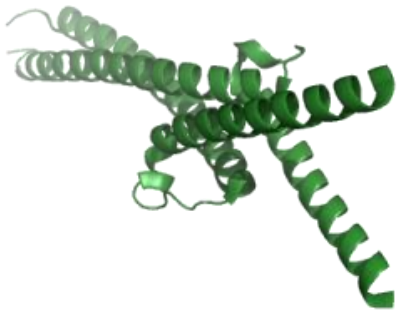
OPPORTUNITY:

- Omomyc ability of inducing DNA damage and impairing DDR could be exploited in combination with PARPi

- Omomyc could restore sensitivity to PARPi in case of intrinsic or acquired resistance

- Omomyc could extend the use of PARPi beyong BRCA-mutant tumors

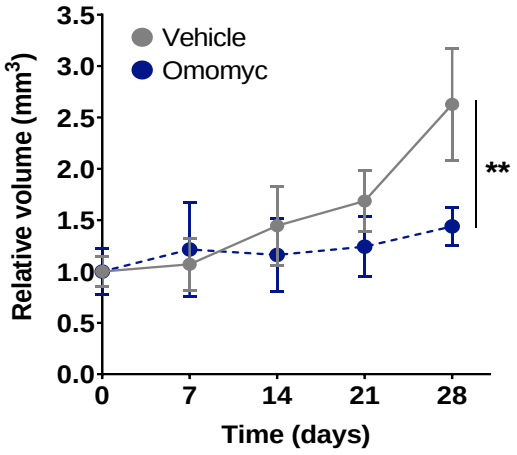
COMBINATION WITH IO



+

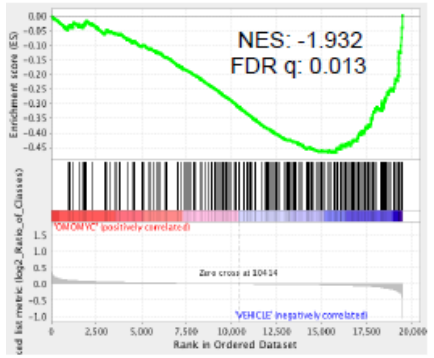
POTENTIAL FOR IO COMBINATION: OMOMYC TURNS COLD TUMORS INTO HOT TUMORS

KRAS^{G12D} NSCLC
2.37mg/kg Omomyc i.n.

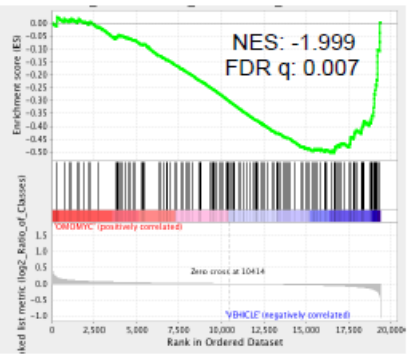


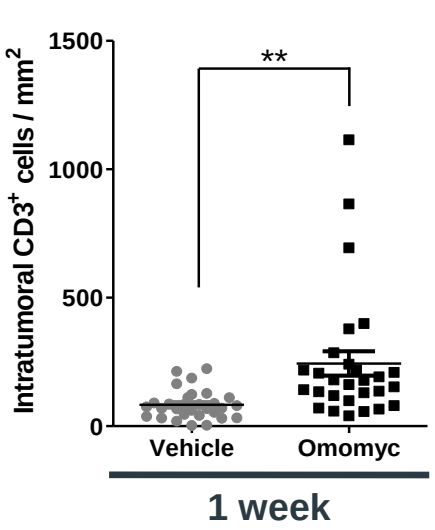
Beaulieu et. al. Sci Trans Med 2019

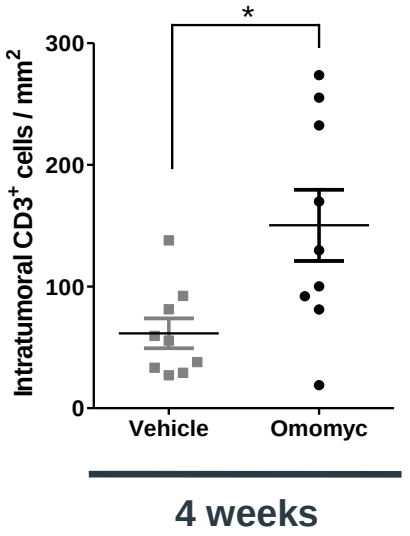
KEGG_CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION



KEGG_CHEMOKINE_SIGNALING_PATHWAY

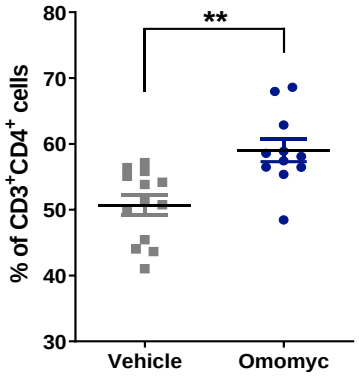




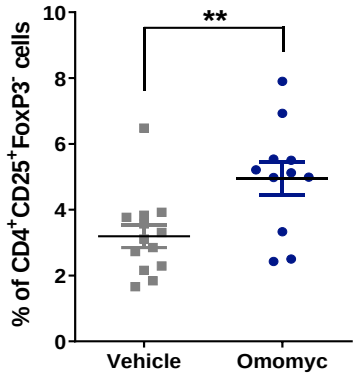


INTRANASAL OMOMYC RECRUITS ACTIVATED T-CELLS WITH A TH1/TH17 PHENOTYPE

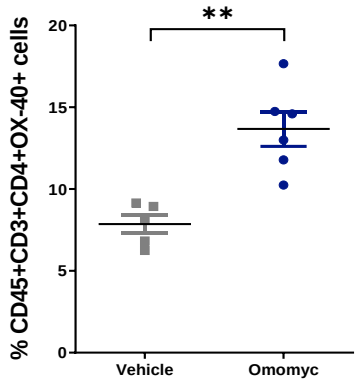
CD4 T cells



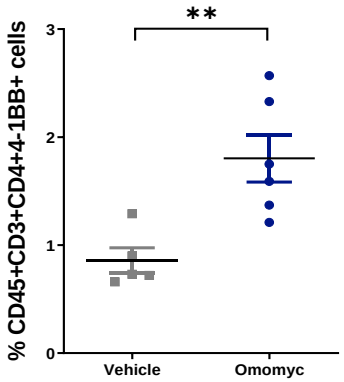
Activated CD4 T cells



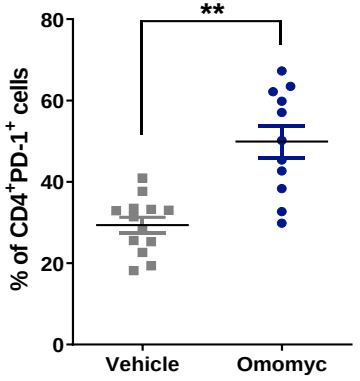
CD4 OX-40+ T cells



CD4 4-1BB+ T cells

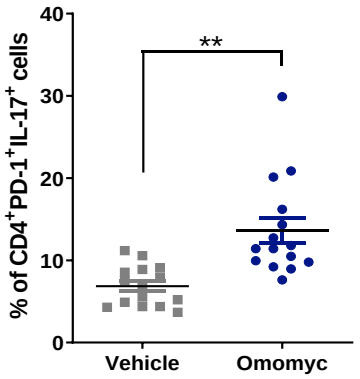


CD4 PD-1+ T cells

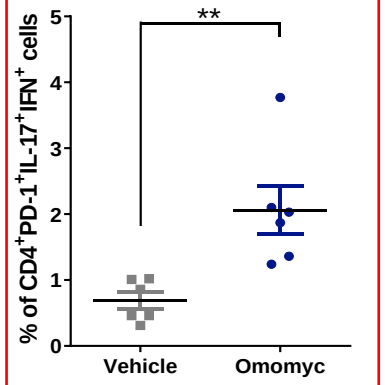


KRAS^{G12D} transgenic model of NSCLC
2.37mg/kg Omomyc i.n.

Th17 cells

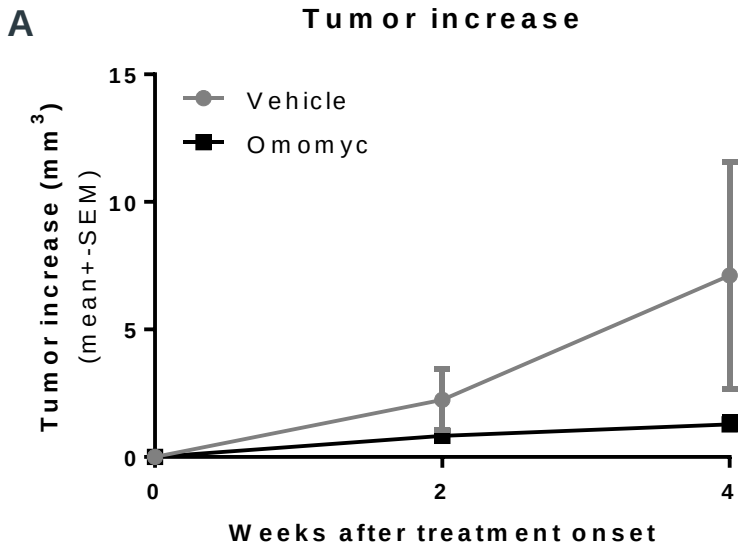


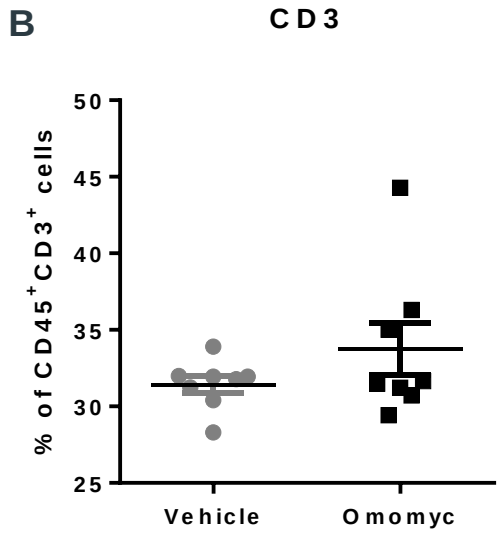
Th1/Th17 cells

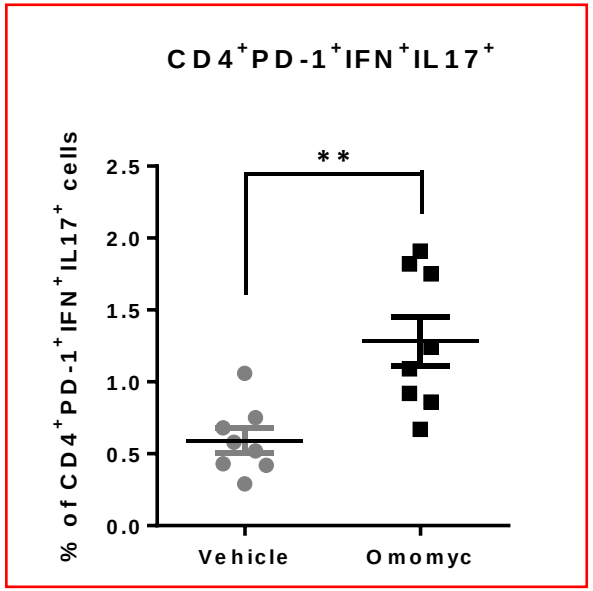


Unpublished data

THE TH1/TH17 PHENOTYPE IS CONFIRMED UPON INTRAVENOUS ADMINISTRATION



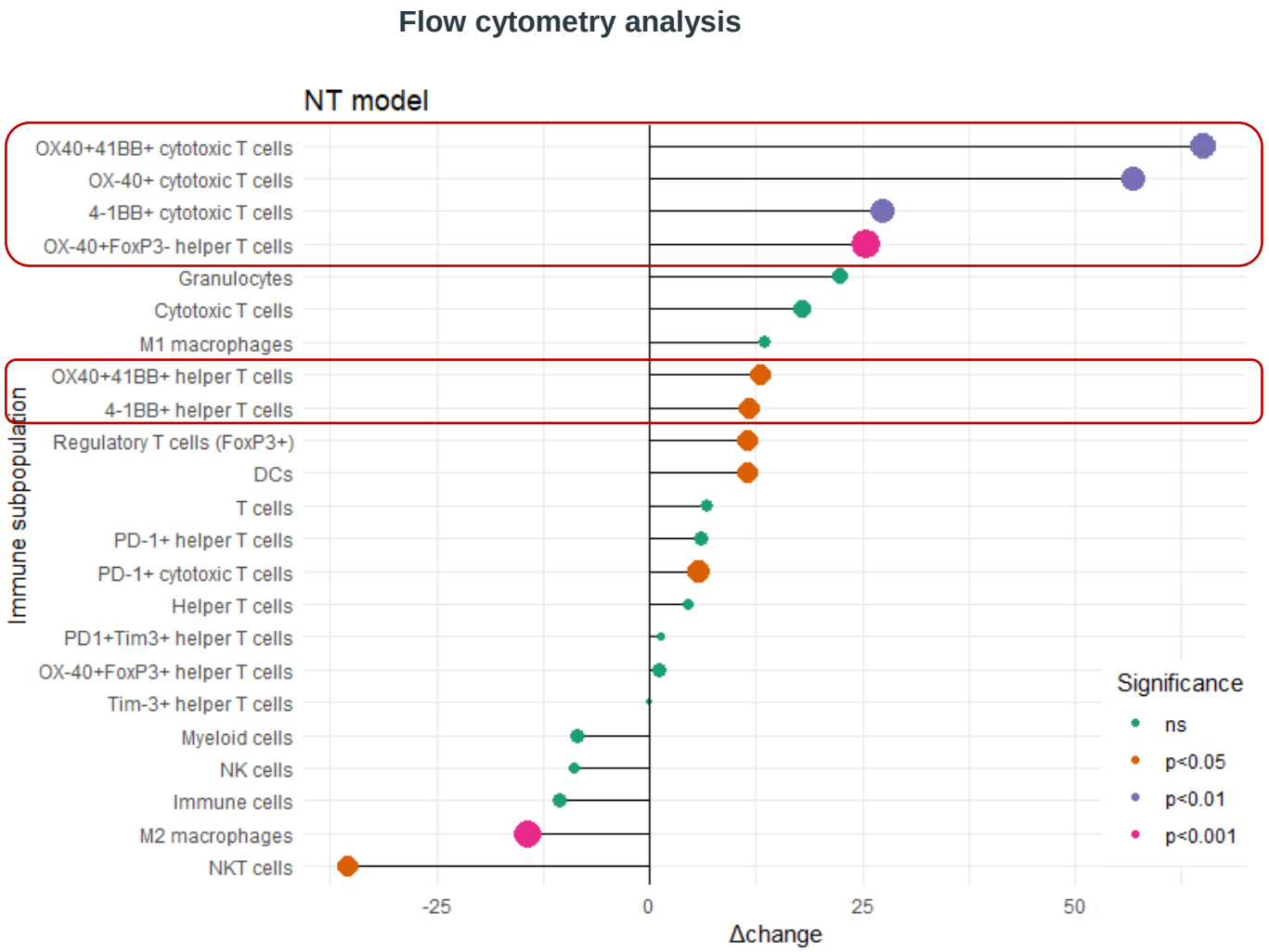


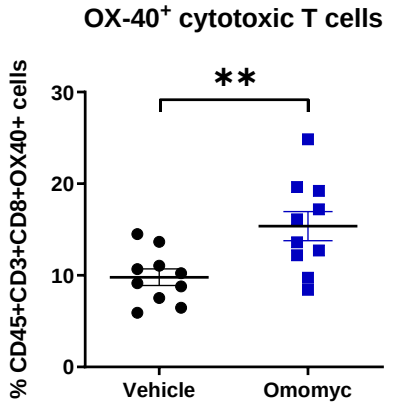


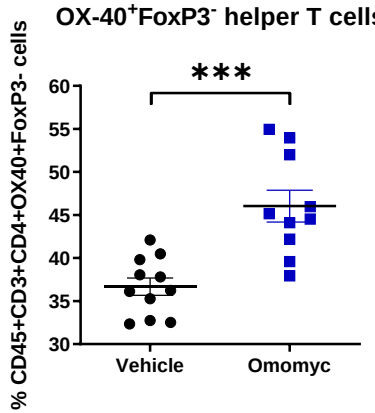
KRAS^{G12D} transgenic model of NSCLC
50mg/kg Omomyc i.v.

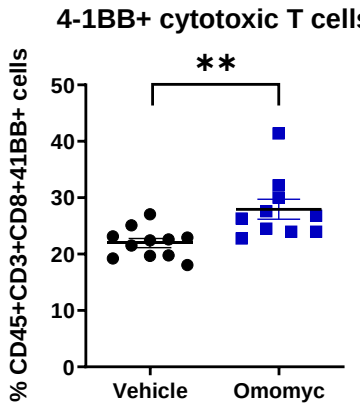
Unpublished data

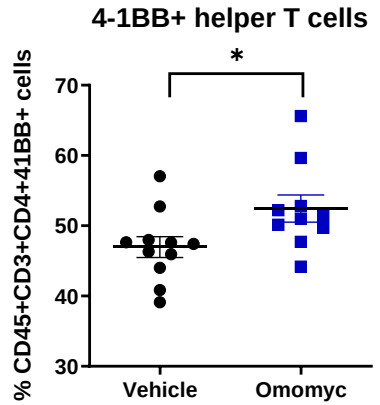
OMOMYC SYSTEMIC TREATMENT INDUCES EXPRESSION OF OX40 and 4-1BB RECEPTORS ON T CELLS

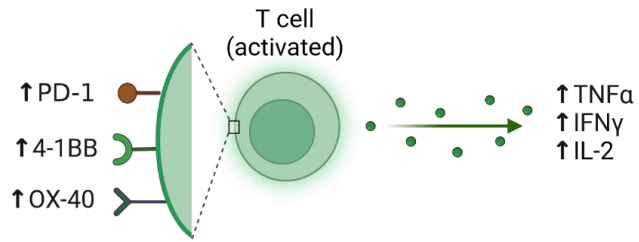












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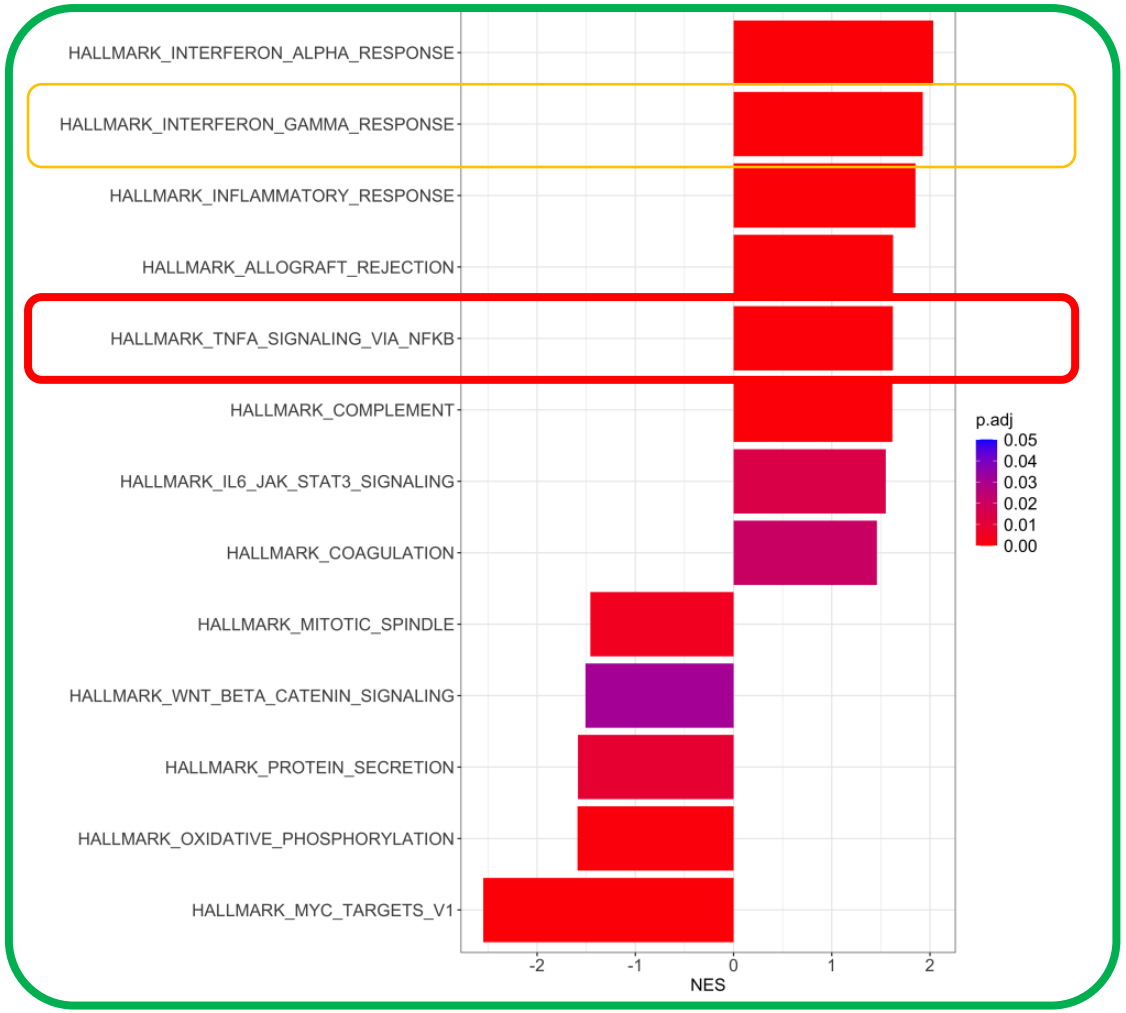
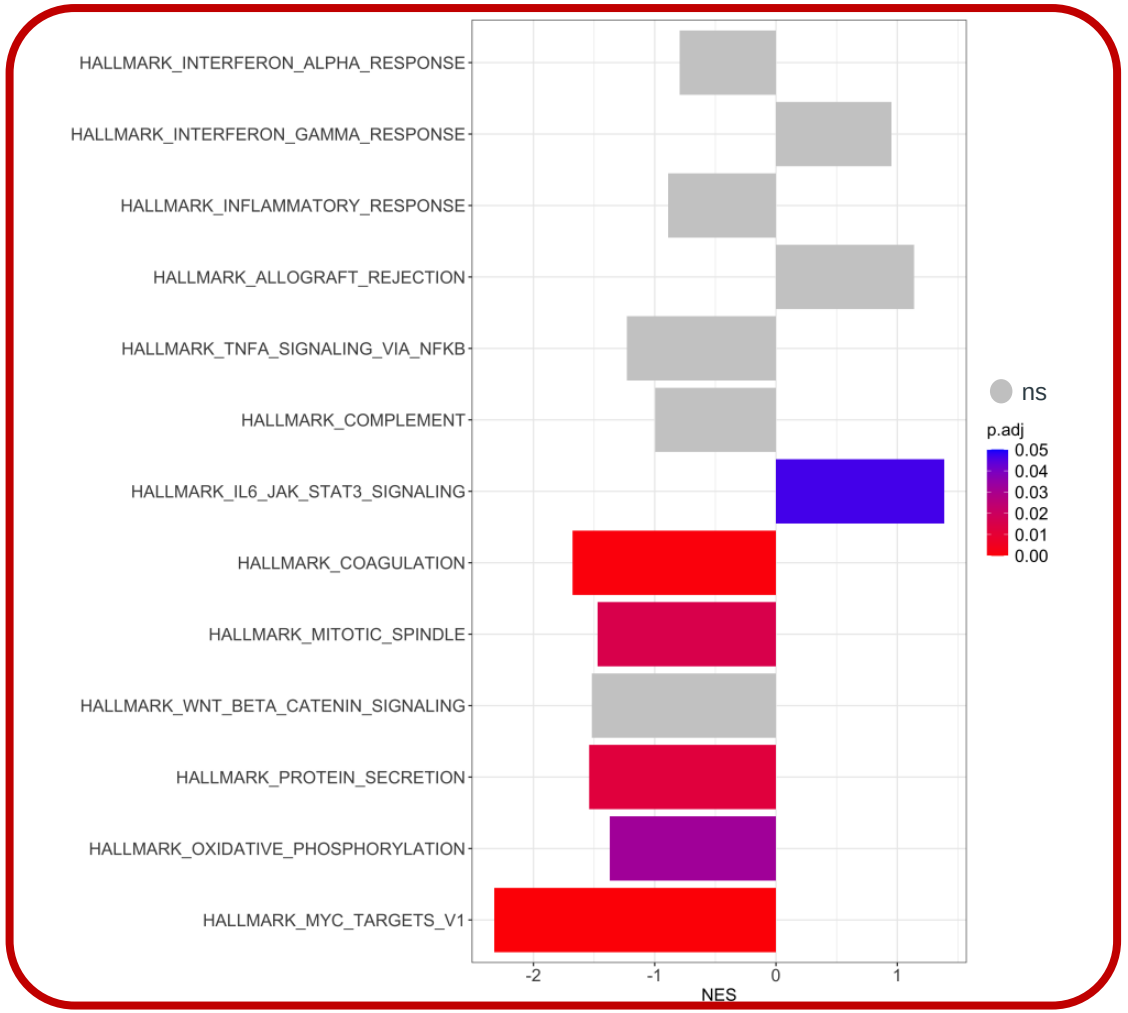
PATIENT BENEFITING FROM OMOMYC TREATMENT HAVE REGULATION OF THE TNF SUPERFAMILY

SD + PR



PD



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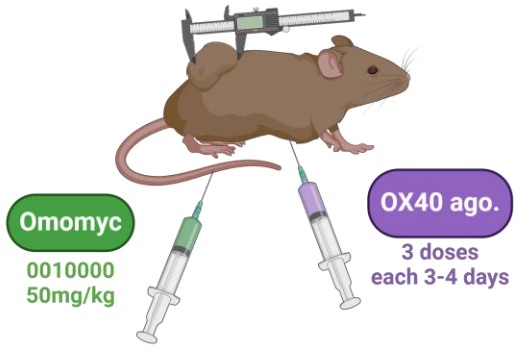
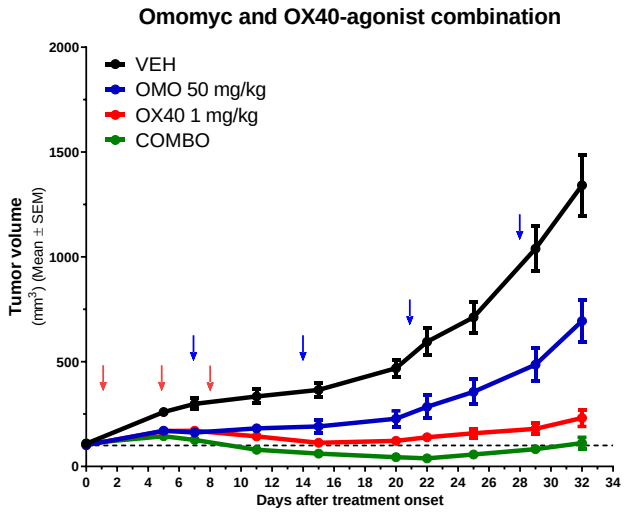
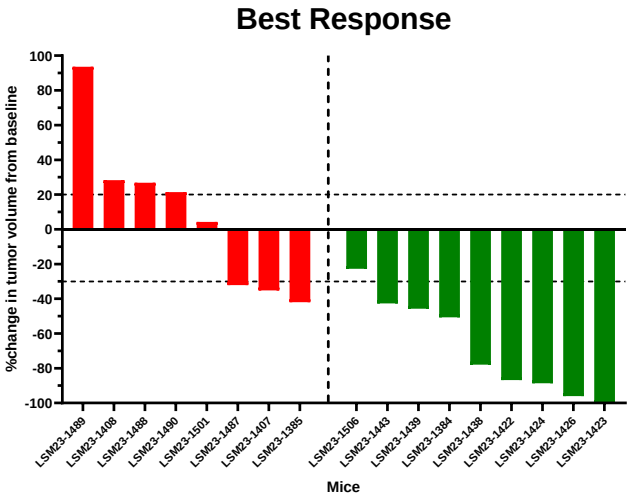
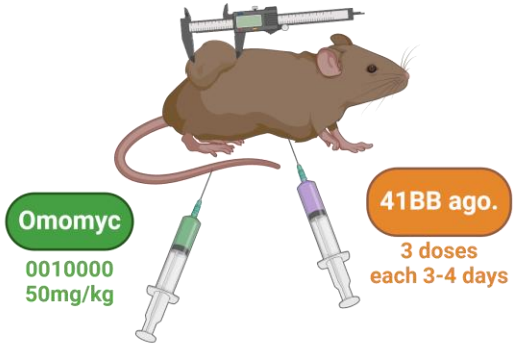
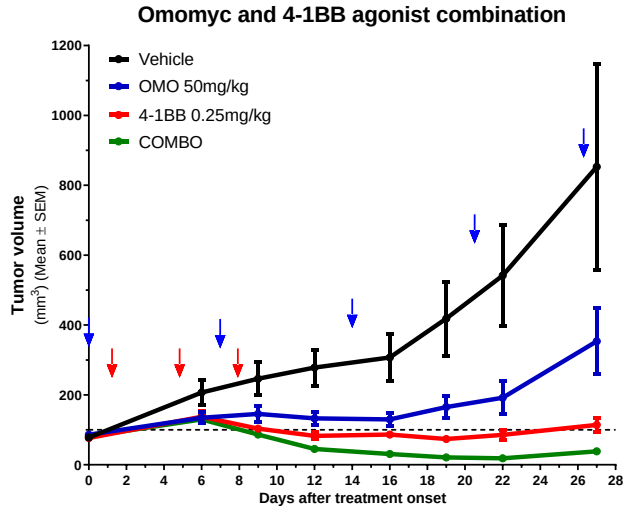
POTENTIAL FOR COMBINATION WITH OX40 AND 4-1BB AGONISTS

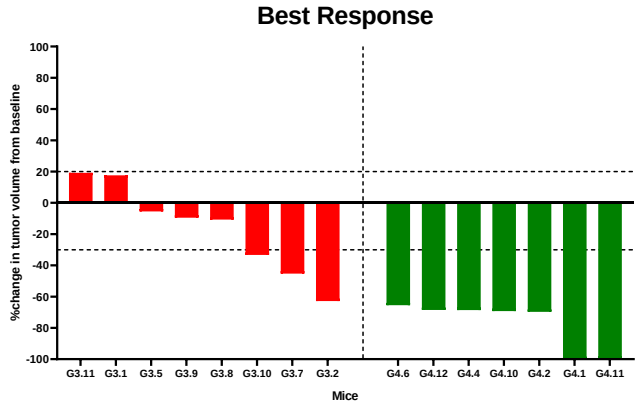












Unpublished data, please do not repost

OPPORTUNITY:

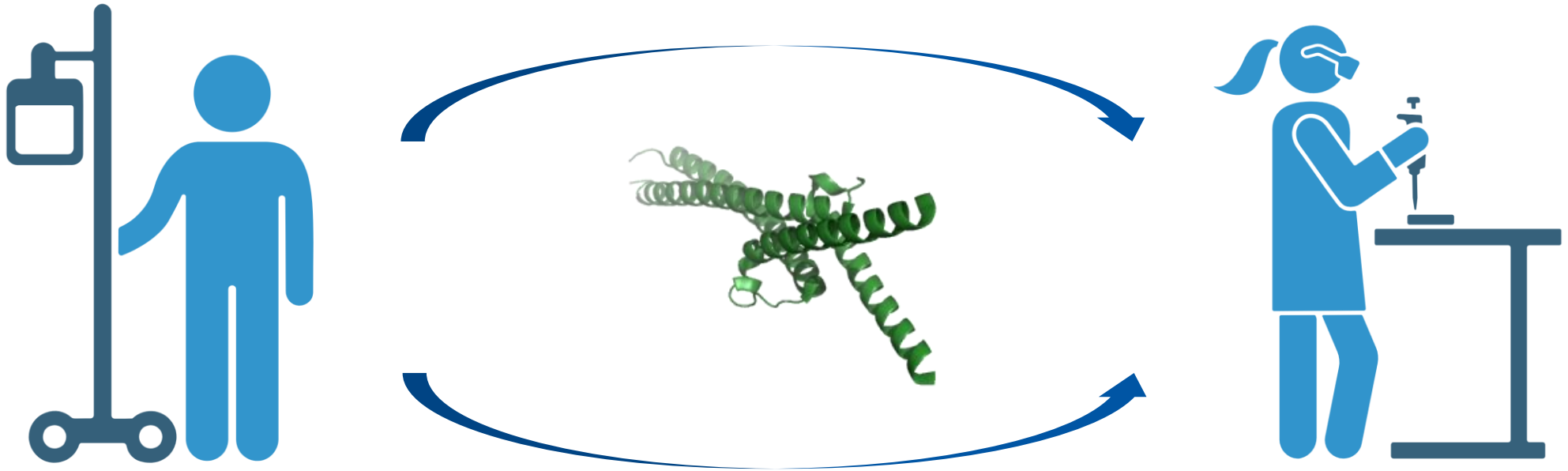
- Omomyc has the ability of turning cold tumors into hot ones

- Omomyc induces an anti-tumor immune microenvironment

- Omomyc could improve the effect of IO therapies

OVERARCHING GOAL

- Provide a viable therapeutic approach for intervention in cancer, offering more efficient and less toxic therapies
- Use our first clinically viable MYC inhibitor as a research tool to further understand MYC biology (and identify other vulnerabilities in cancer).



ACKNOWLEDGEMENTS

… and patients, families and clinicians