A Comparative Understanding of Oncogenic MYC Signaling in the Metastatic Tumor Immune Microenvironment

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FACTOR 2025

FLINT ANIMAL CANCER CENTER
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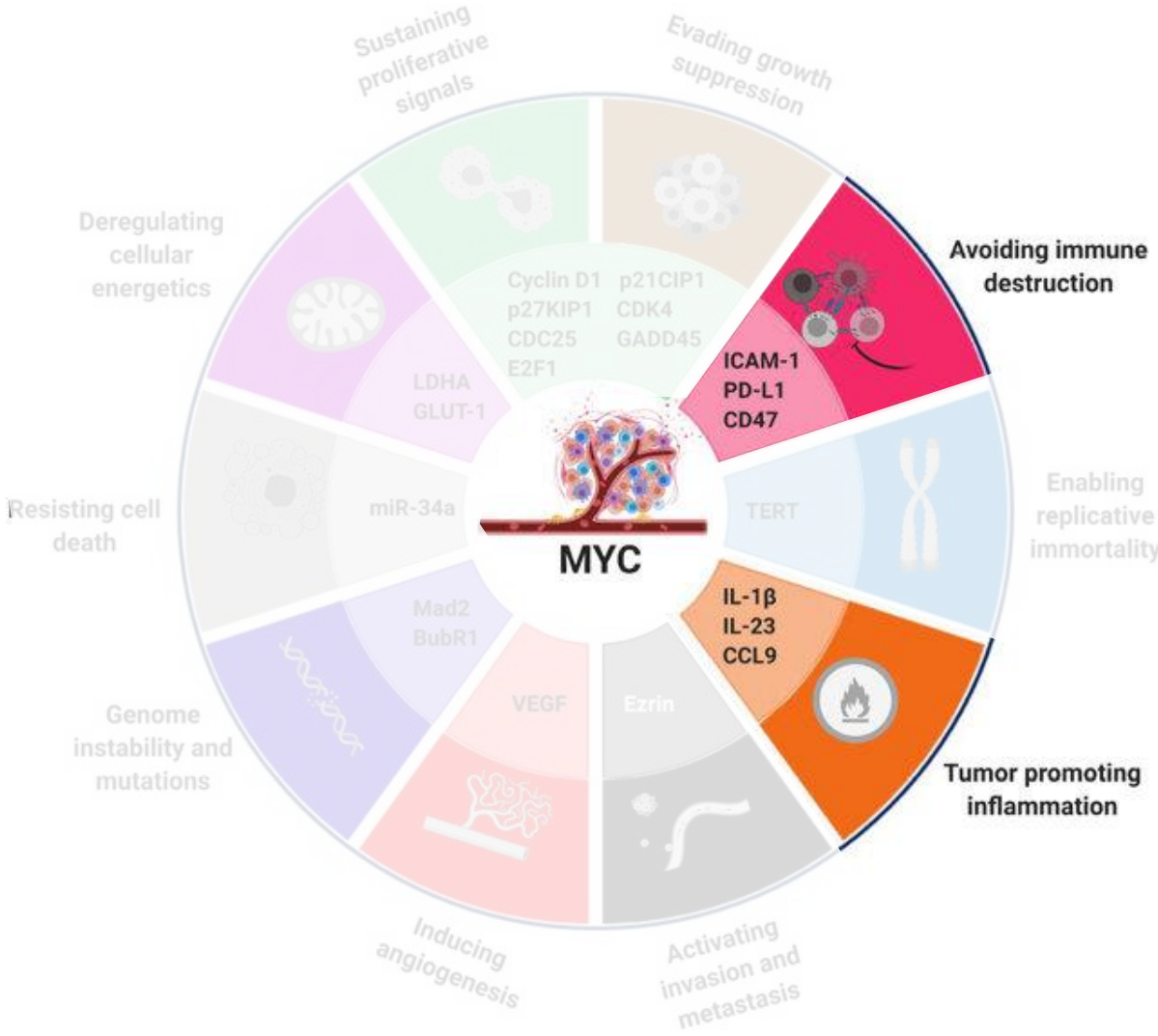
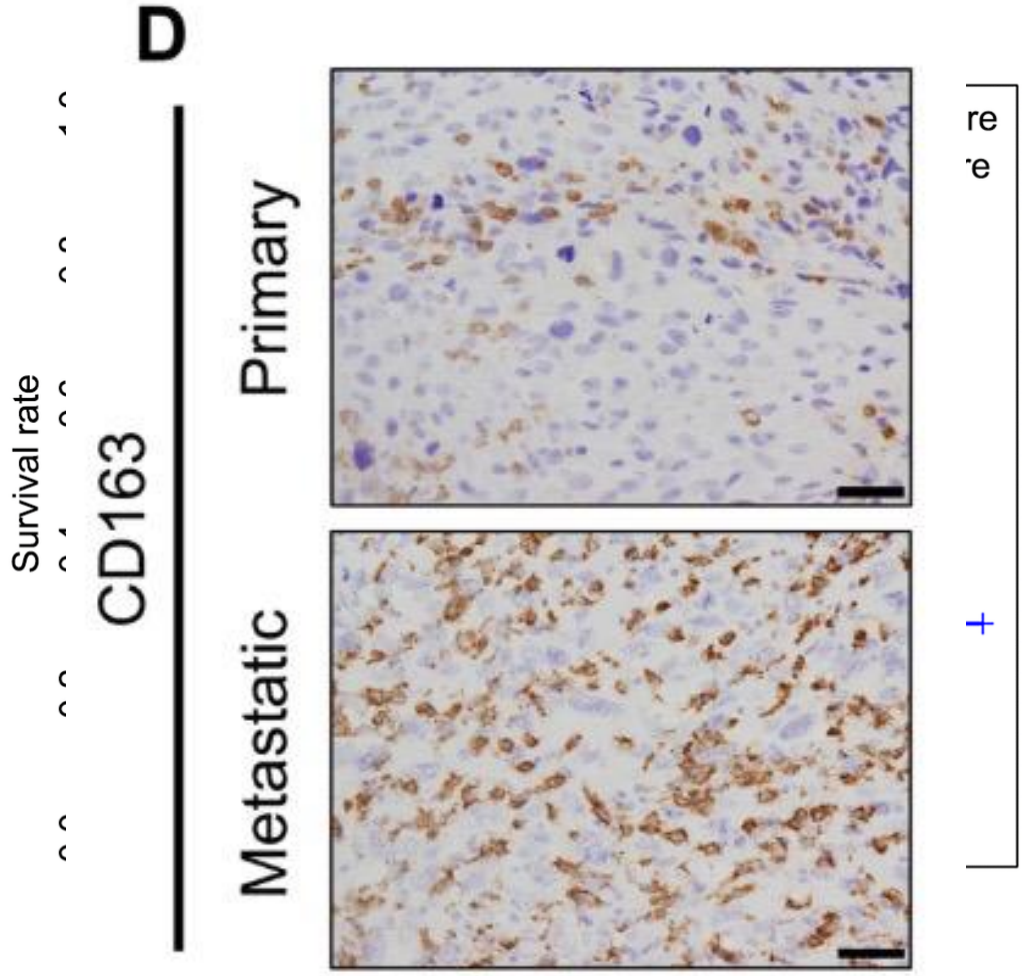
MYC in the Tumor Microenvironment (TME)

- MYC is a master transcription factor
- Cancer cell survival advantage with overexpression
  - Genomic amplification confers poor prognosis in osteosarcoma (OS)
- Role in cancer immune regulation:
  - Increased tumor associated macrophages (TAM)
  - Decreased T cells



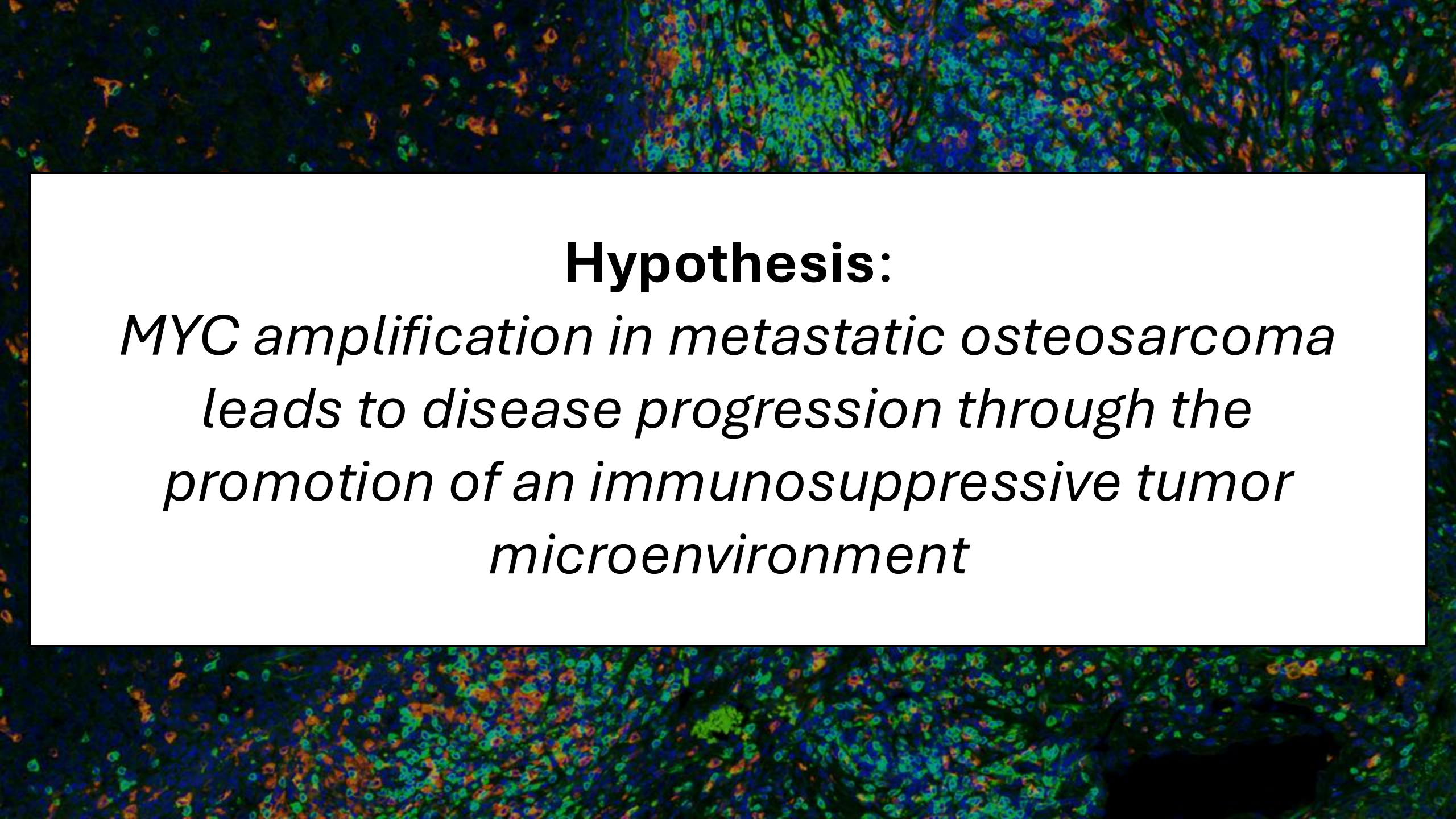
Martinez-Martin & Soucek. Cancer Drug Resist. 2021

Metastatic OS is immunosuppressive



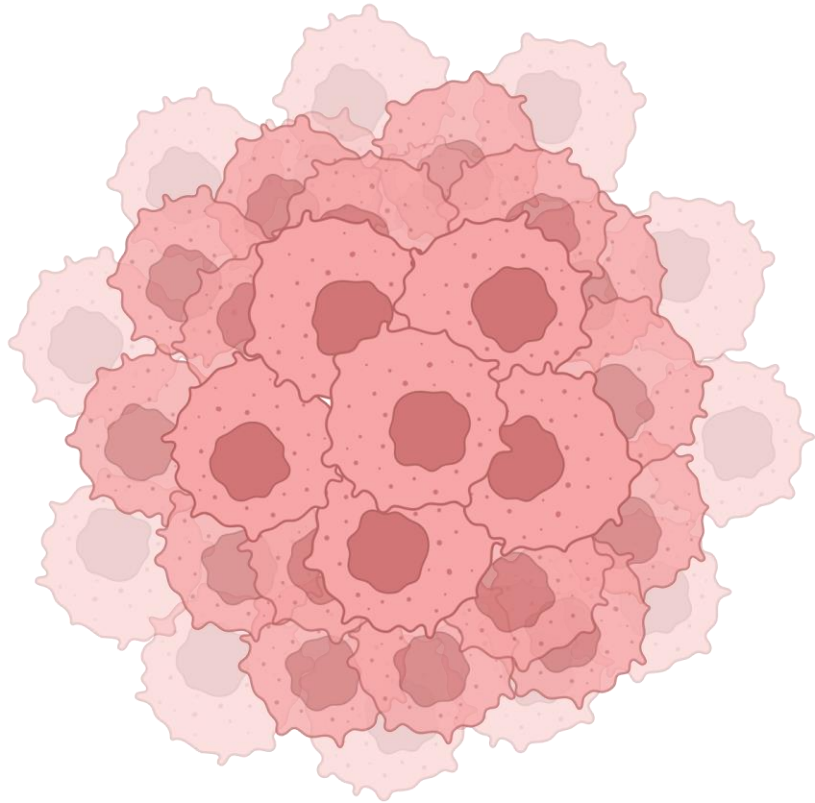
- Enriched with TAMs
- Poor T cell infiltration
- Poor response to immunotherapy
- Low effector immune infiltration confers worse prognosis

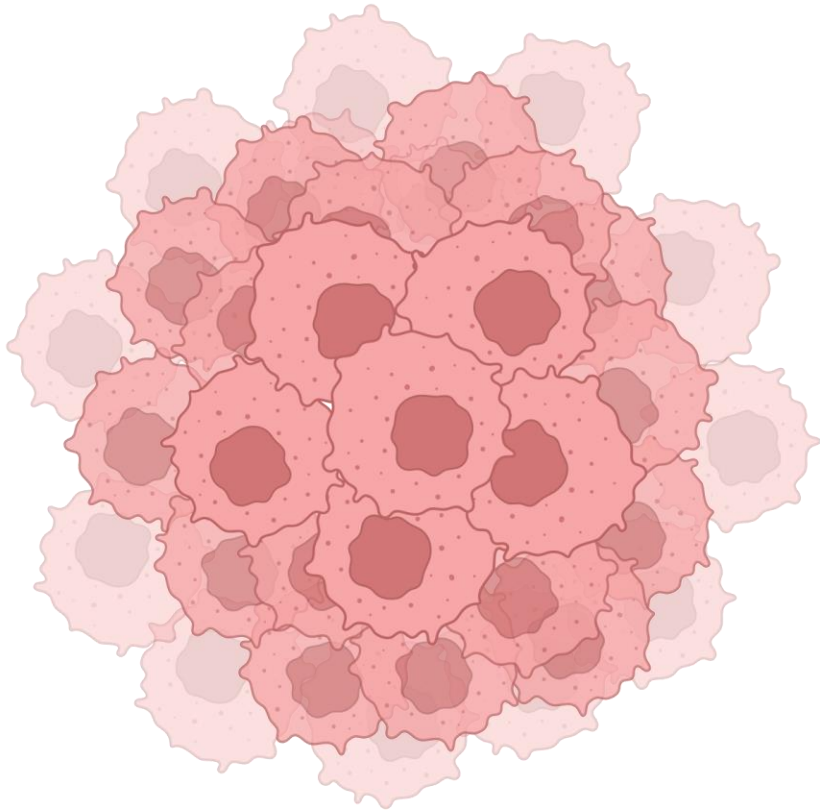
Tatsuno et al. Cell Death & Disease 2024



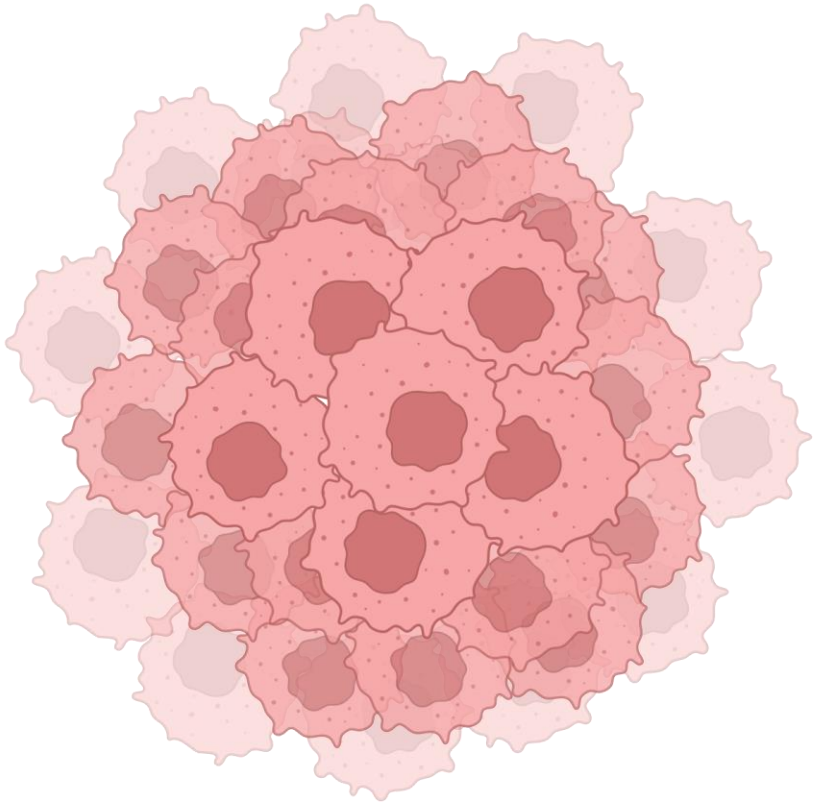
Hypothesis:

MYC amplification in metastatic osteosarcoma leads to disease progression through the promotion of an immunosuppressive tumor microenvironment

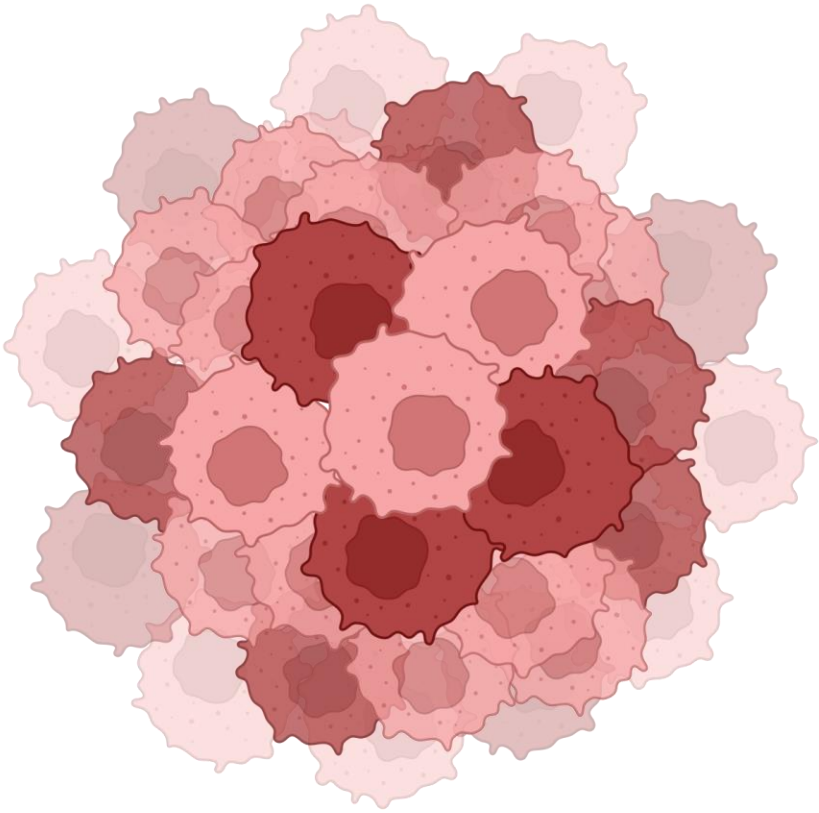




MYC Low



MYC High

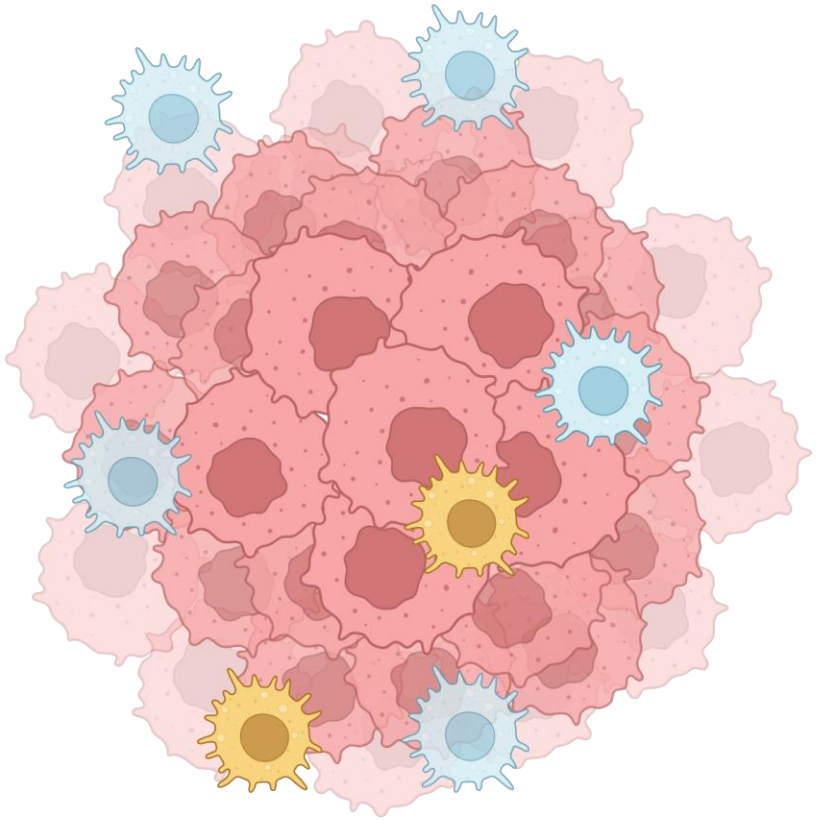


Tumor Cells

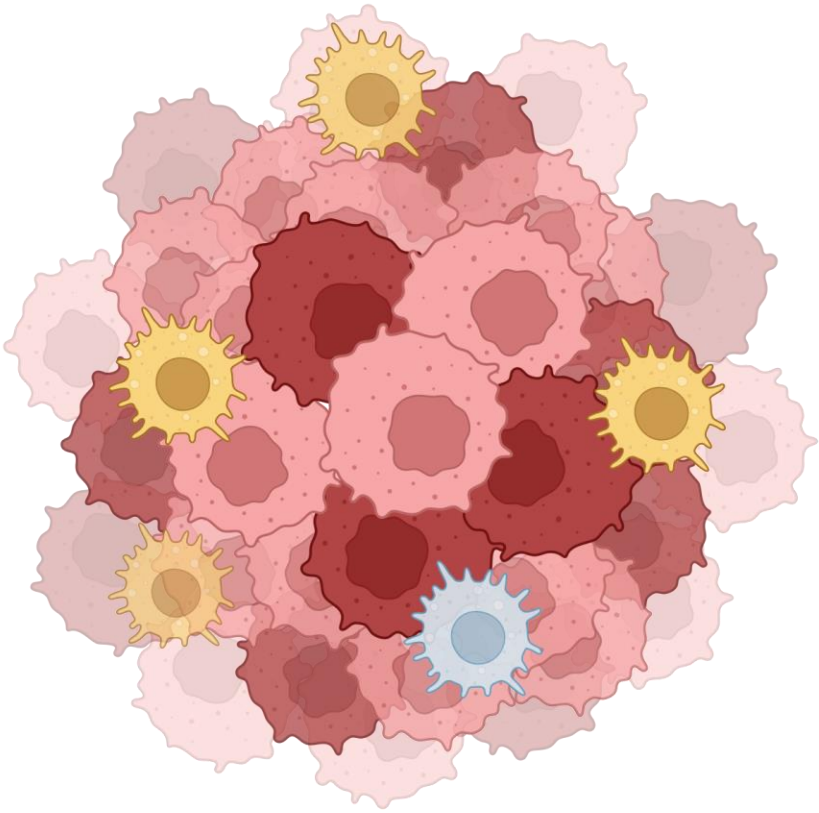
Low or Normal MYC

MYC Hyperactive

MYC Low



MYC High



Tumor Cells

Low or Normal MYC

MYC Hyperactive

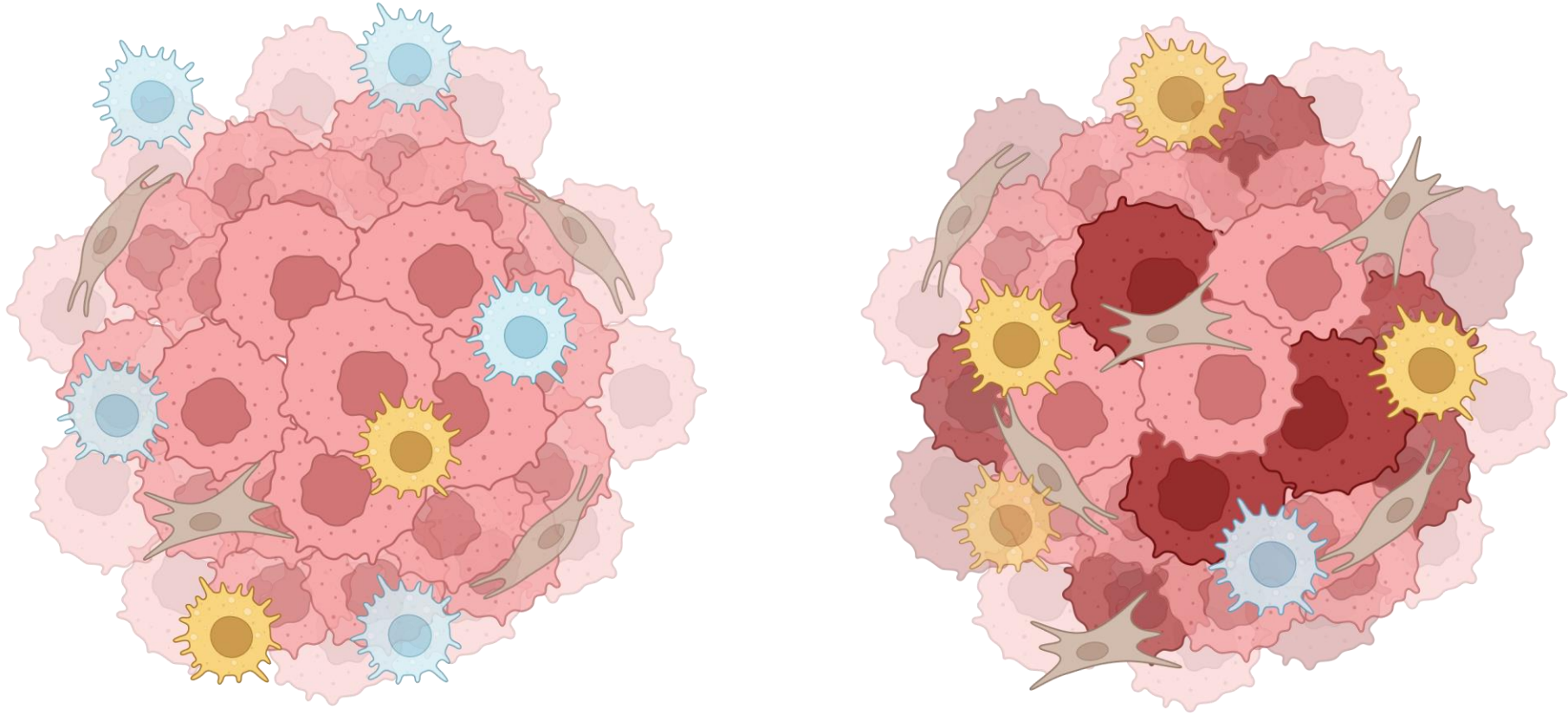
Tumor Associated Macrophages

Pro-Inflammatory

Immunosuppressive

MYC Low

MYC High



Tumor Associated Fibroblasts

Quiescent

Activated

Tumor Cells

Low or Normal MYC

MYC Hyperactive

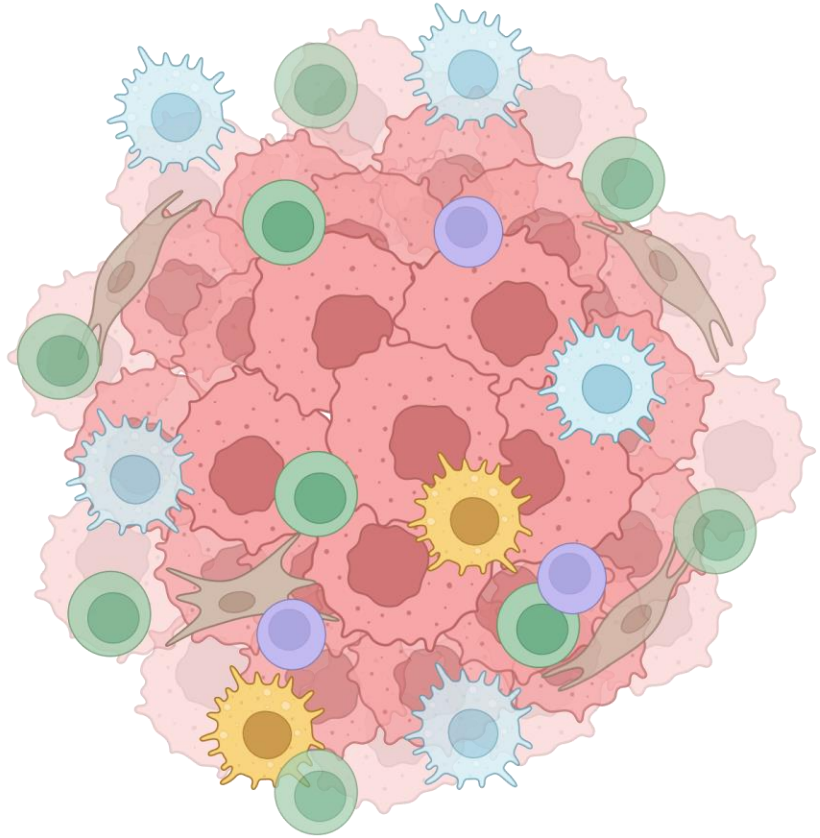
Tumor Associated Macrophages

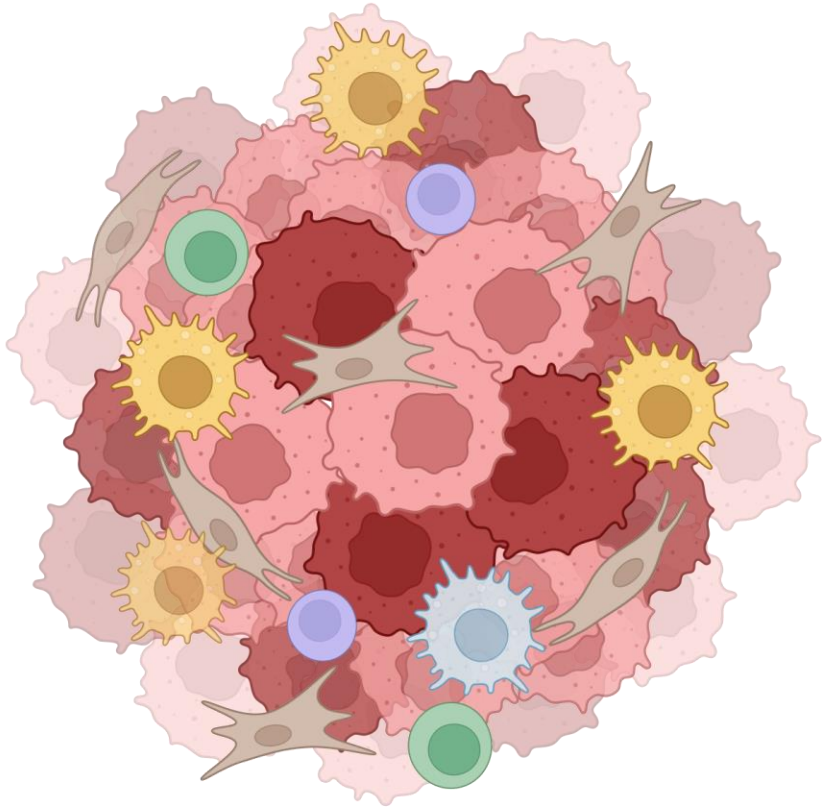
Pro-Inflammatory

Immunosuppressive

MYC Low

MYC High





Tumor Associated Fibroblasts

Quiescent

Activated

Tumor Cells

Low or Normal MYC

MYC Hyperactive

Tumor Associated Macrophages

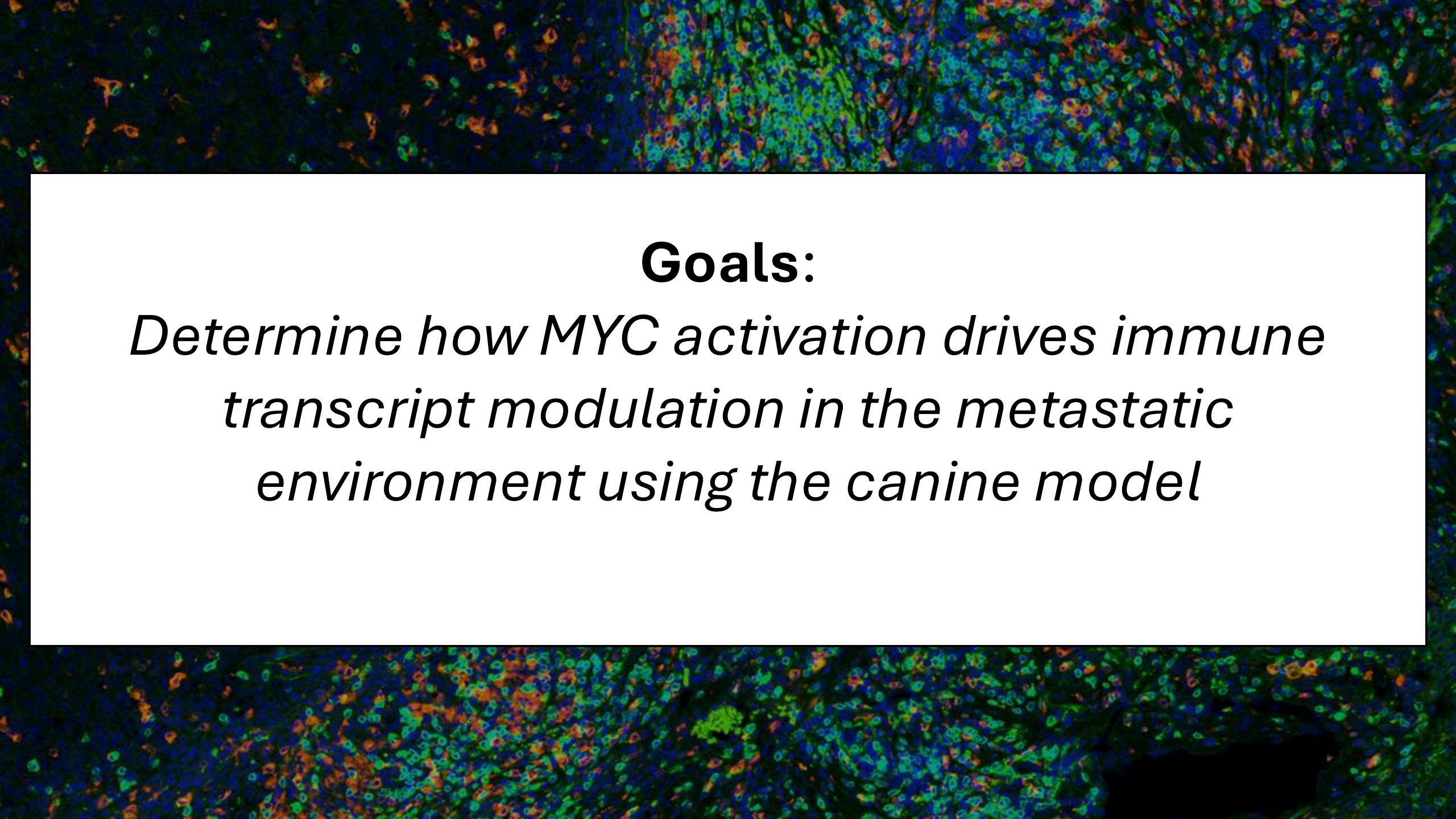
Pro-Inflammatory

Immunosuppressive

T Cells

Effector

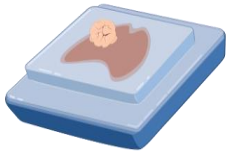
Exhausted



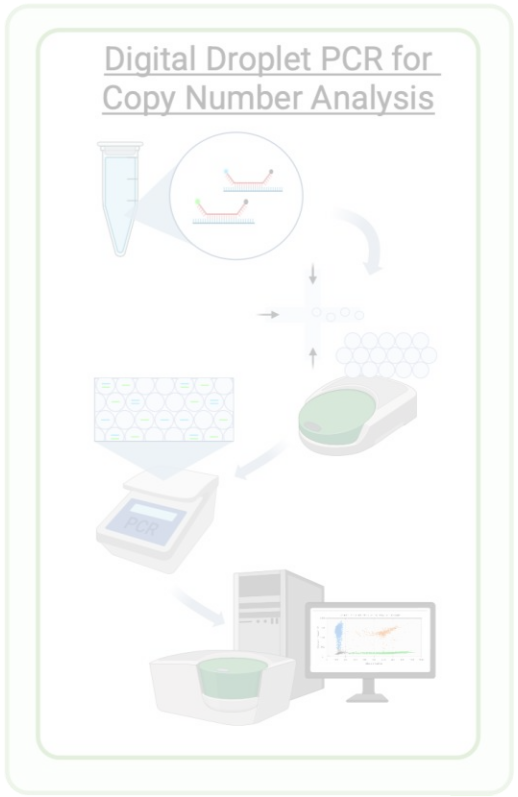
Goals:

Determine how MYC activation drives immune transcript modulation in the metastatic environment using the canine model

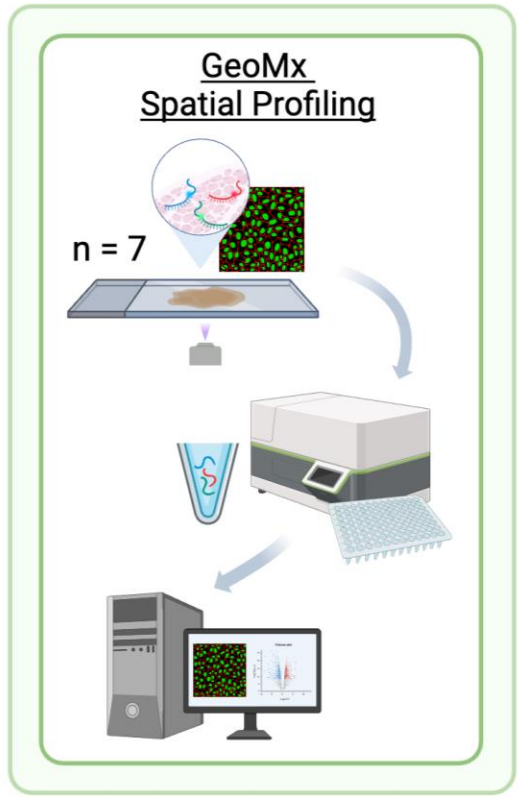
Methods



42 archived FFPE canine OS pulmonary metastases



DNA



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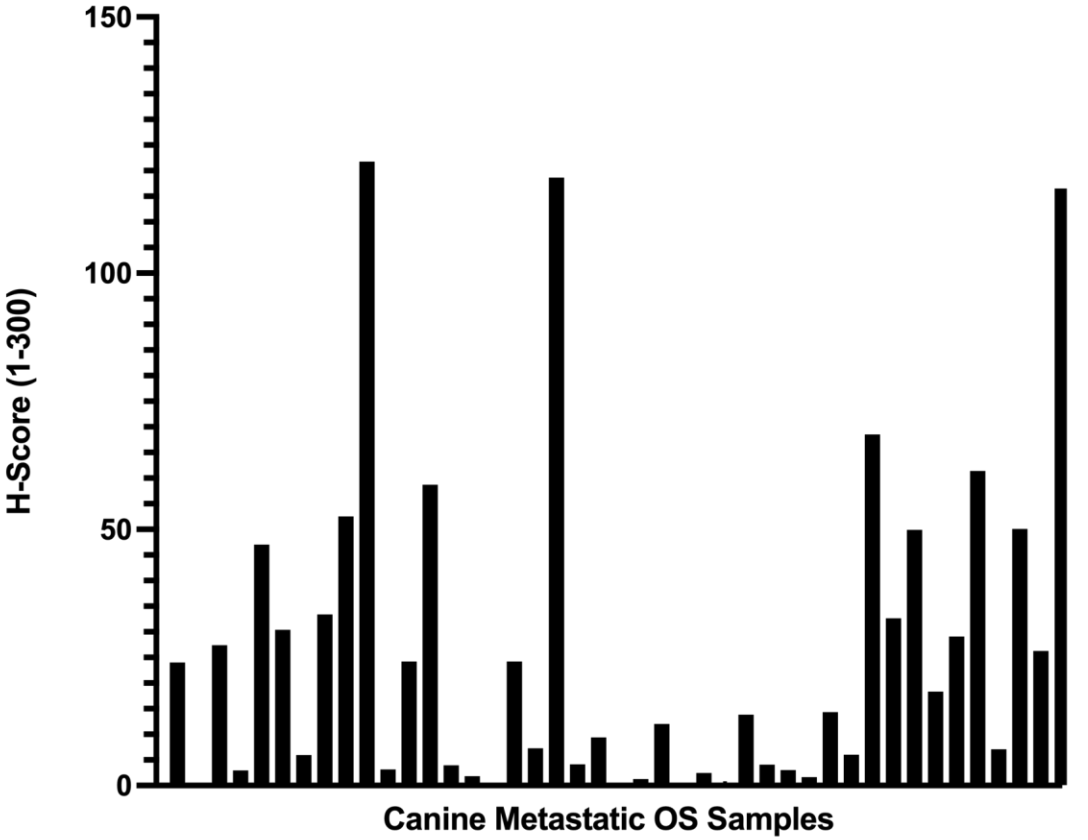
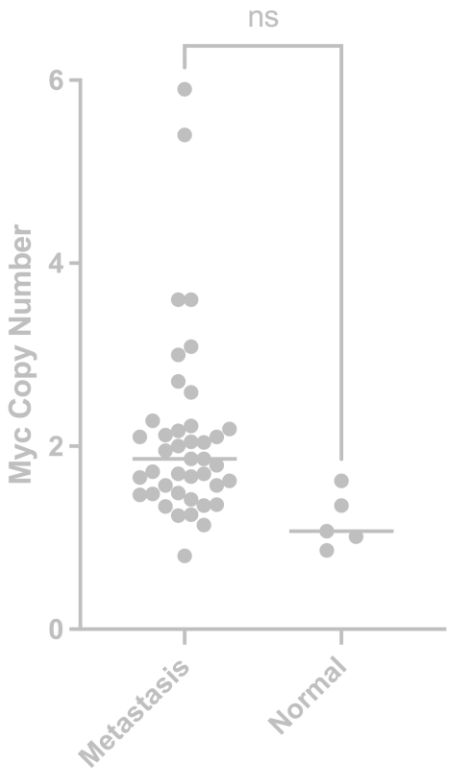
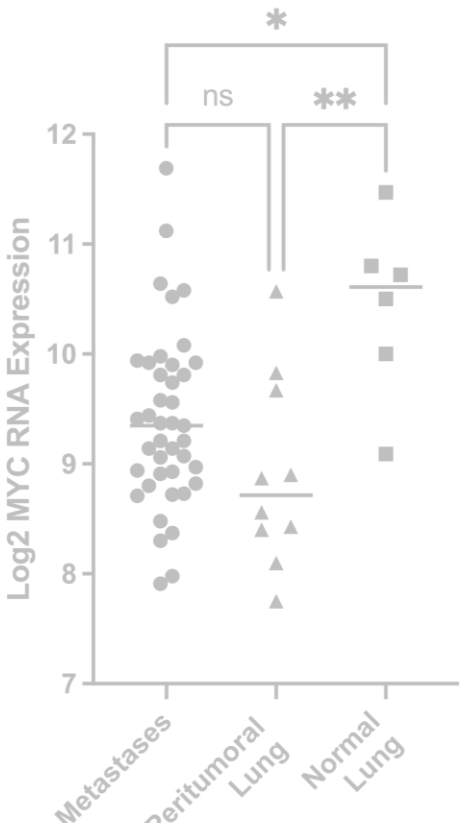
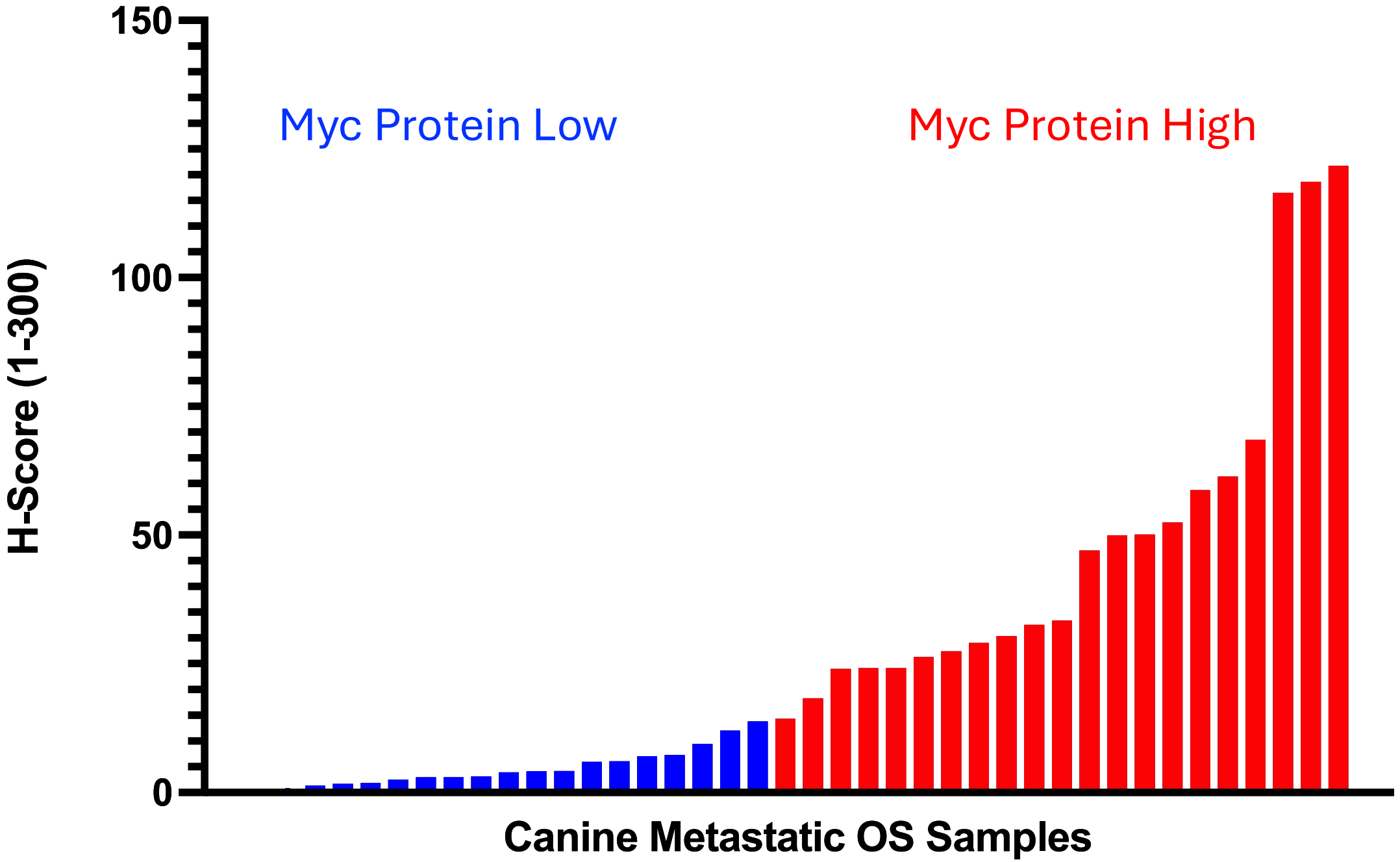
MYC is overexpressed in metastatic canine OS – but this is not driven by genomic amplification



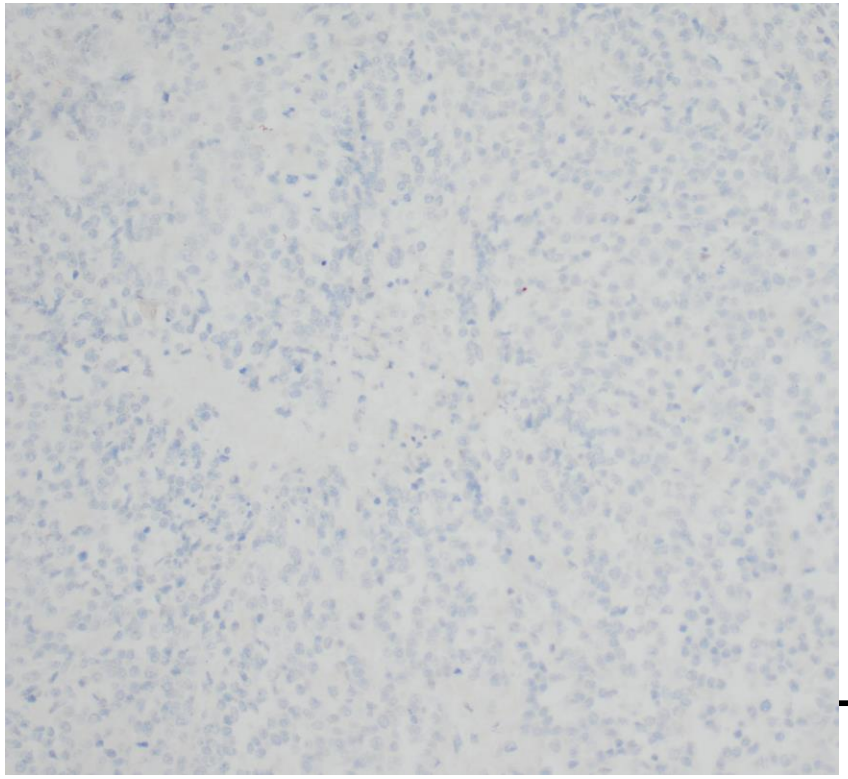
Protein

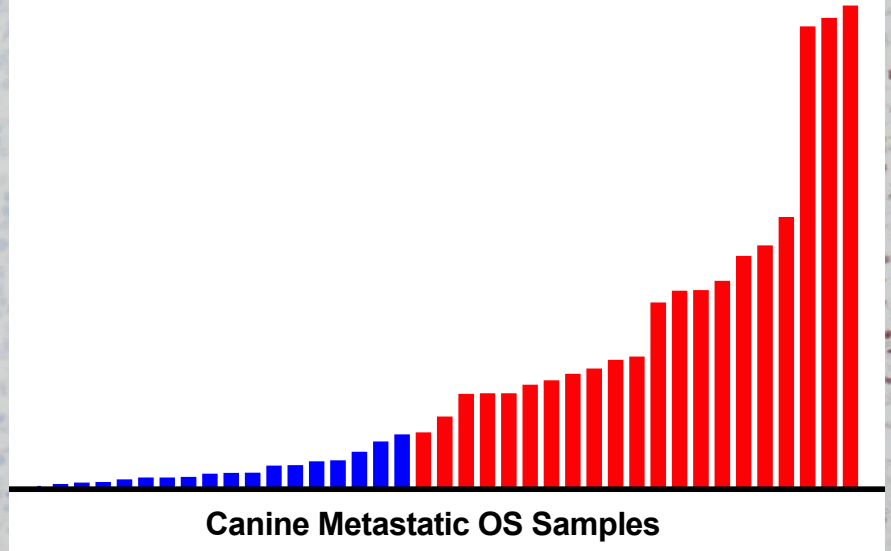




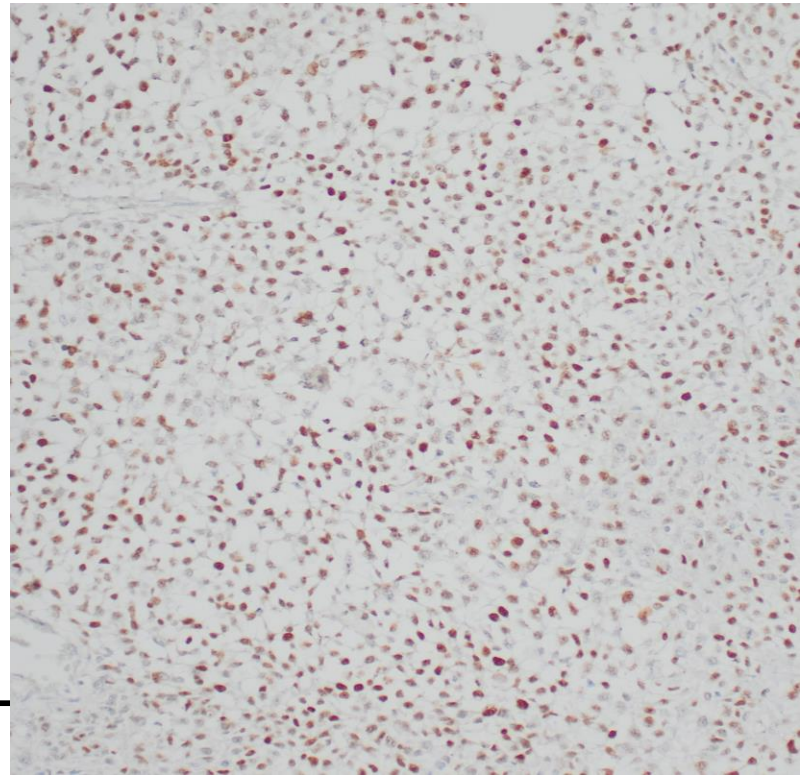

150
100
50
0
H-Score (1-300)
Myc Protein Low
Myc Protein High
Canine Metastatic OS Samples

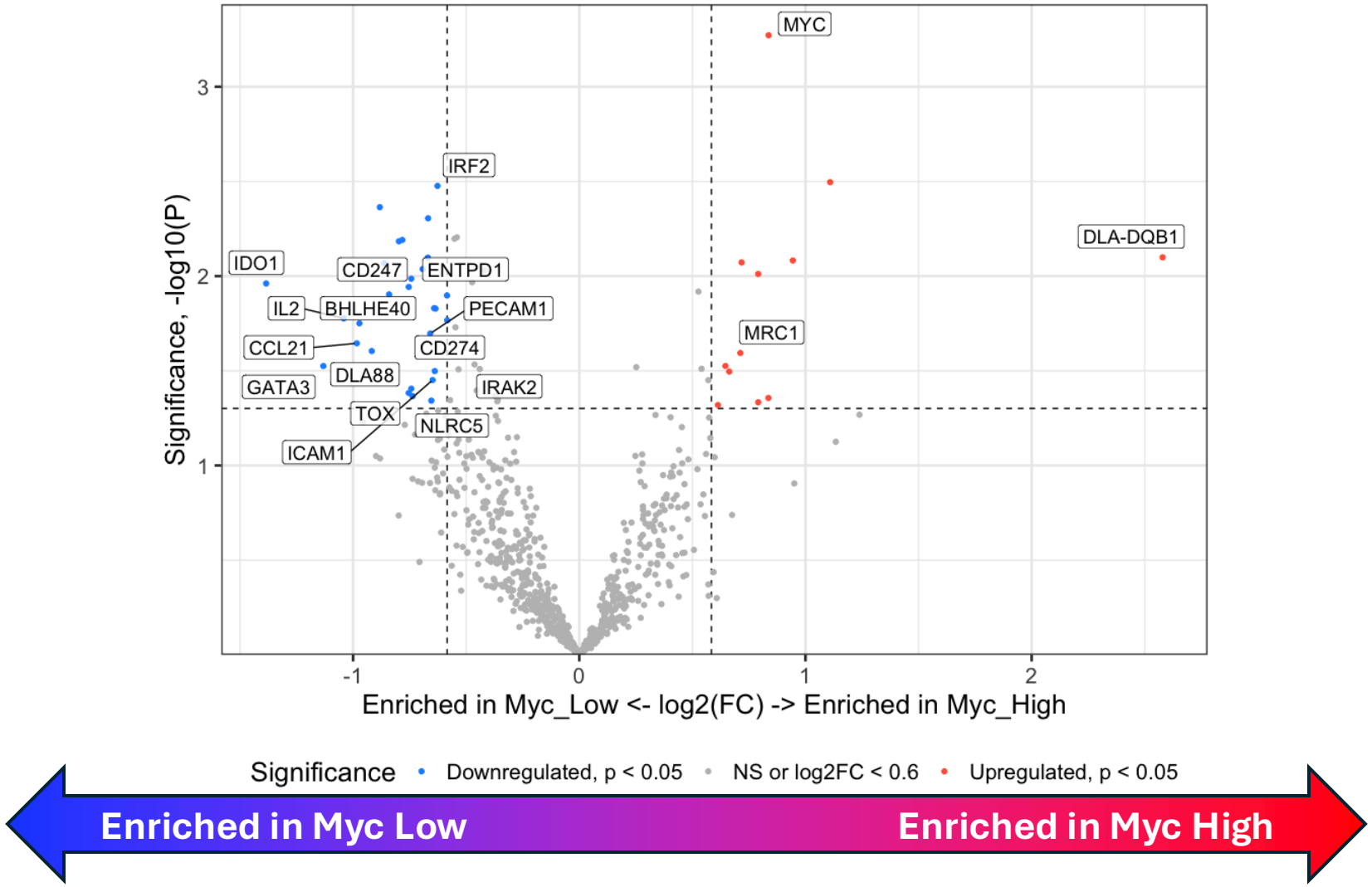
Myc Protein Low



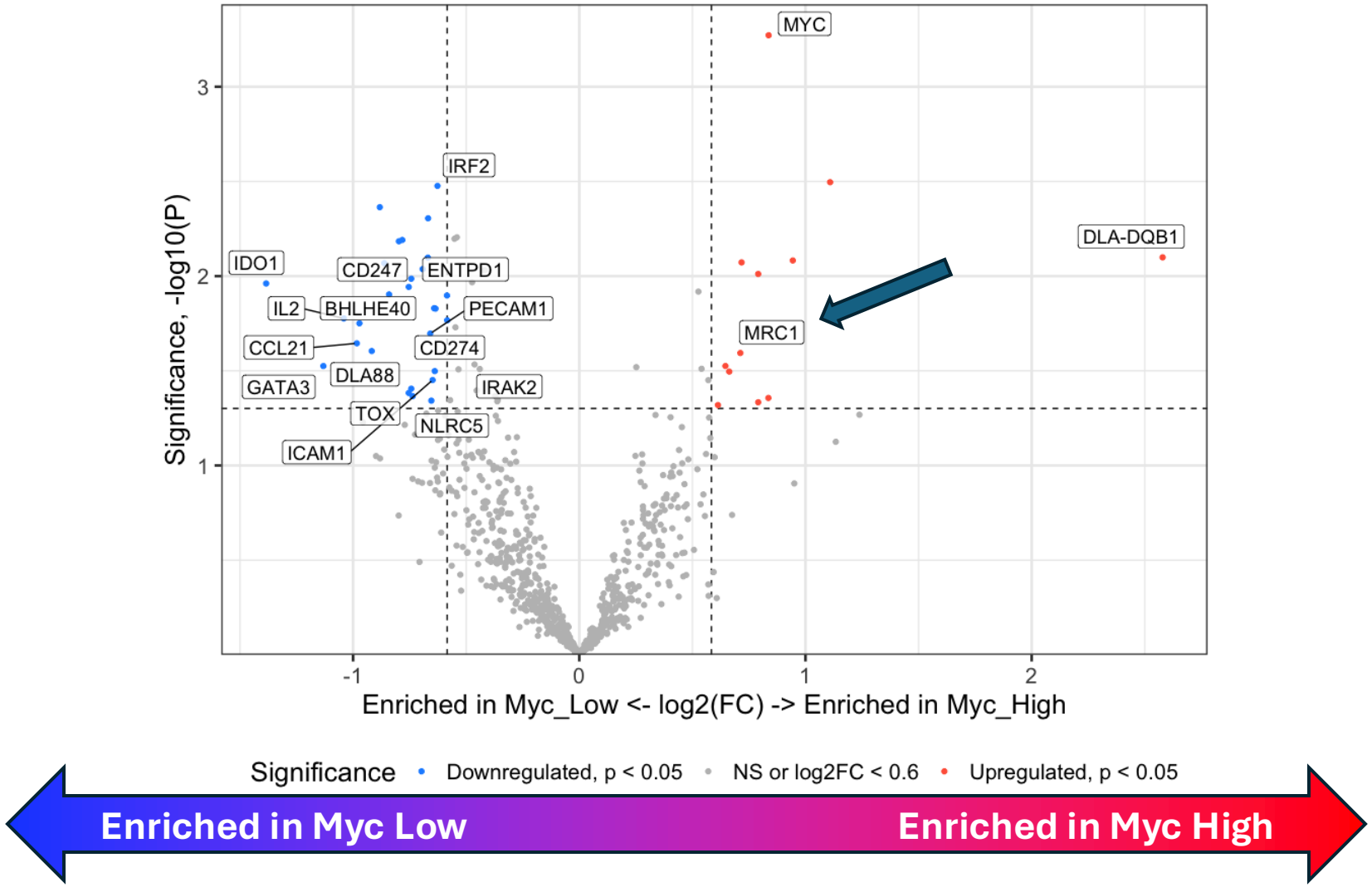


Myc Protein High

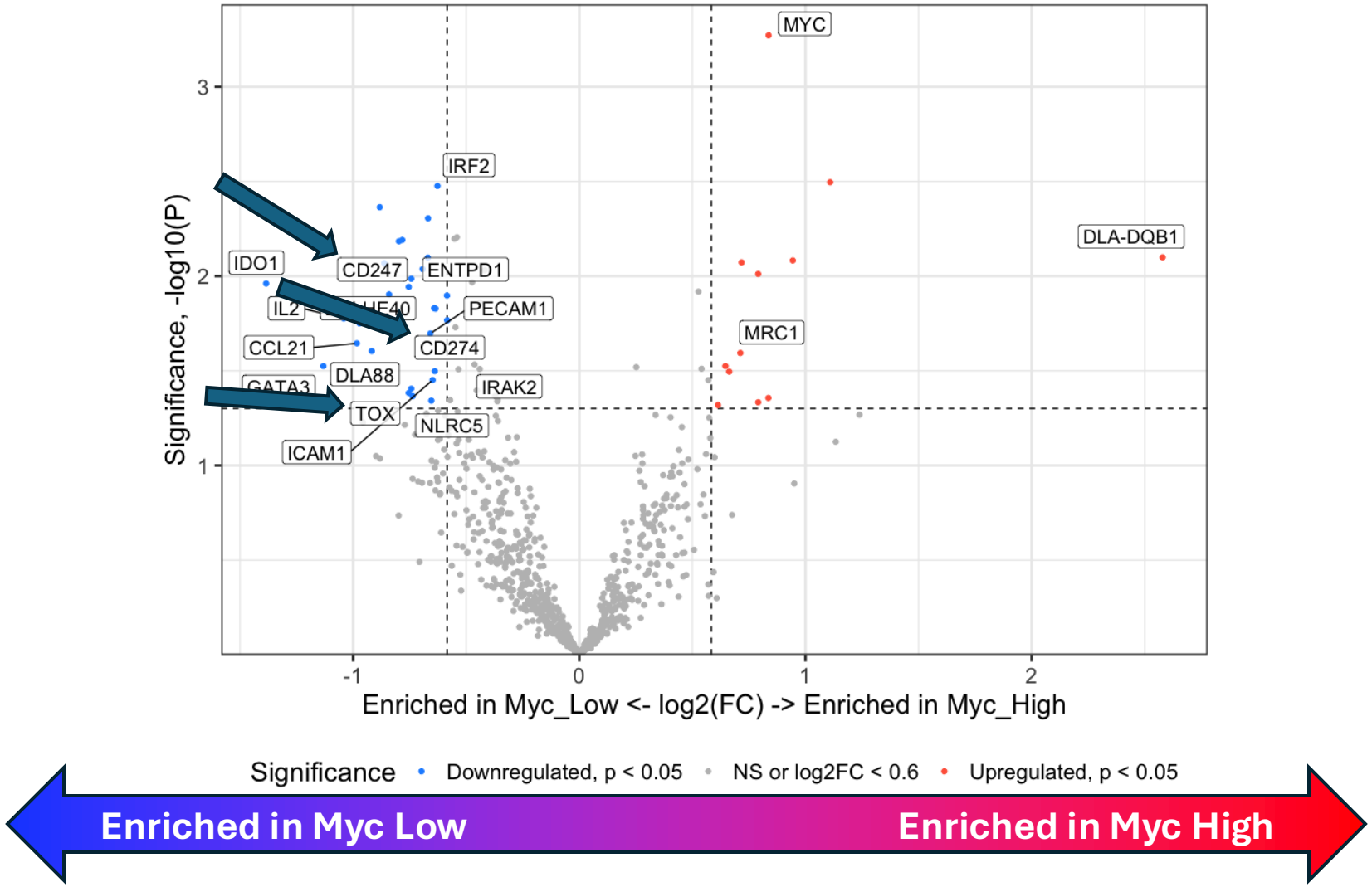



MYC
IRF2
DLA-DQB1
IDO1
CD247
ENTPD1
IL2
BHLHE40
PECAM1
MRC1
CCL21
CD274
DLA88
GATA3
IRAK2
TOX
NLRC5
ICAM1
Significance, -log10(P)
3
2
1
-1
0
1
2
Enriched in Myc_Low <- log2(FC) -> Enriched in Myc_High
Significance
Downregulated, p < 0.05
NS or log2FC < 0.6
Upregulated, p < 0.05
Enriched in Myc Low
Enriched in Myc High

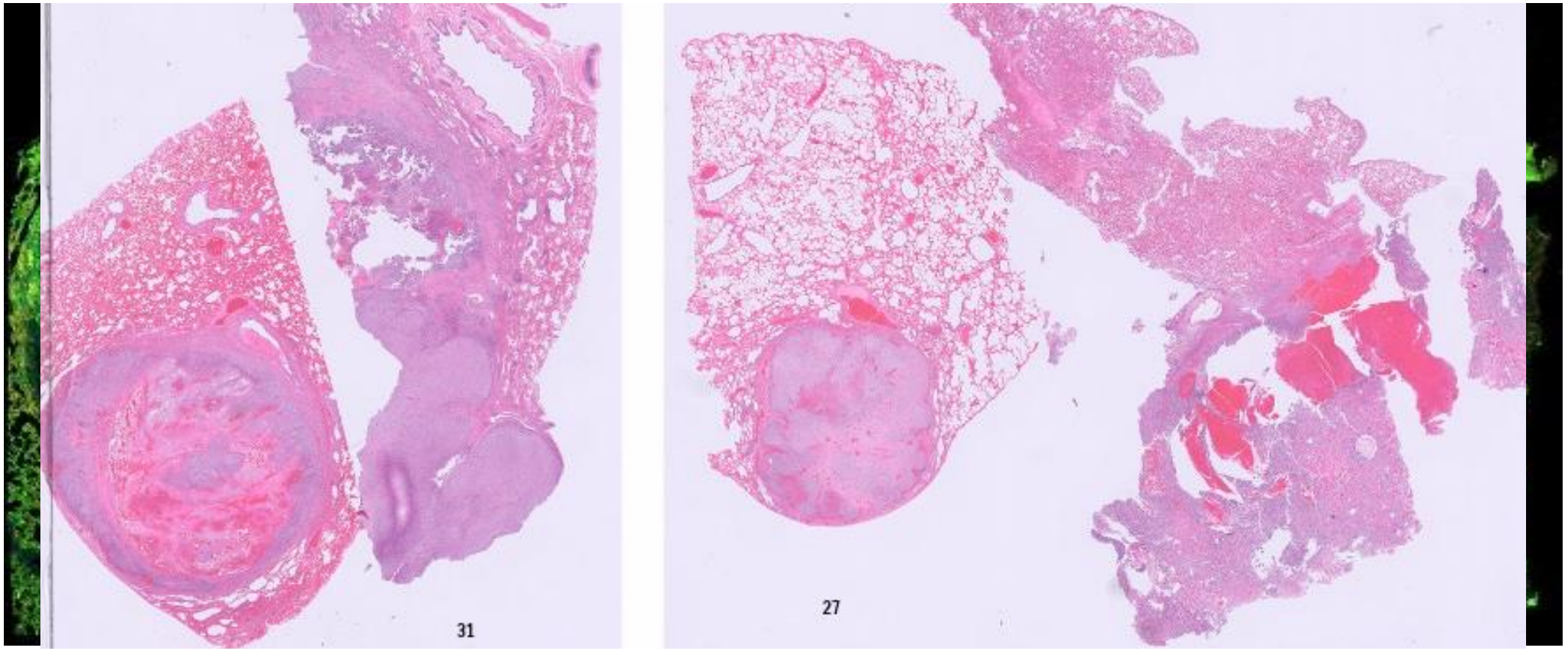
High MYC samples are enriched for immunosuppressive macrophage marker MRC1 (CD206)

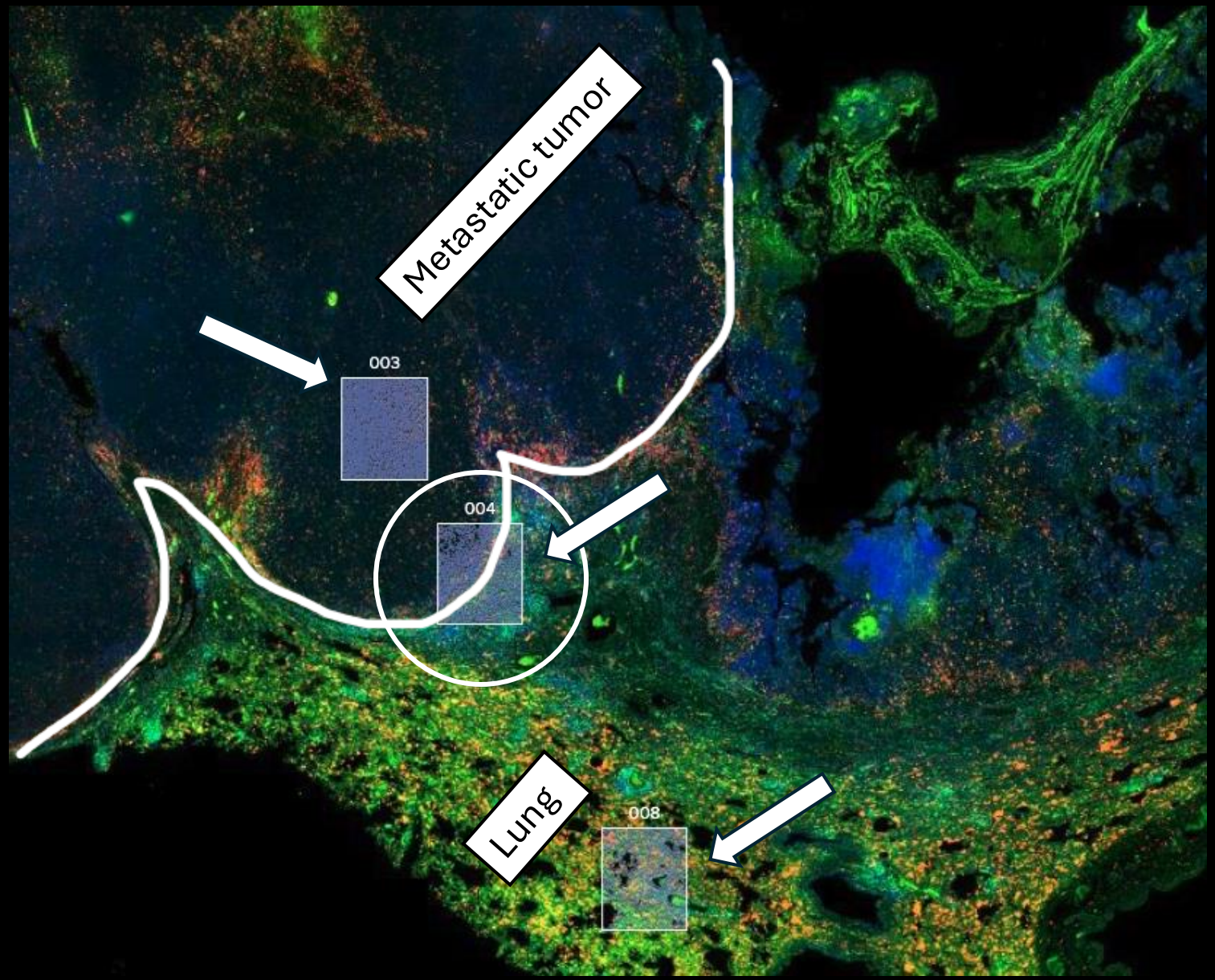


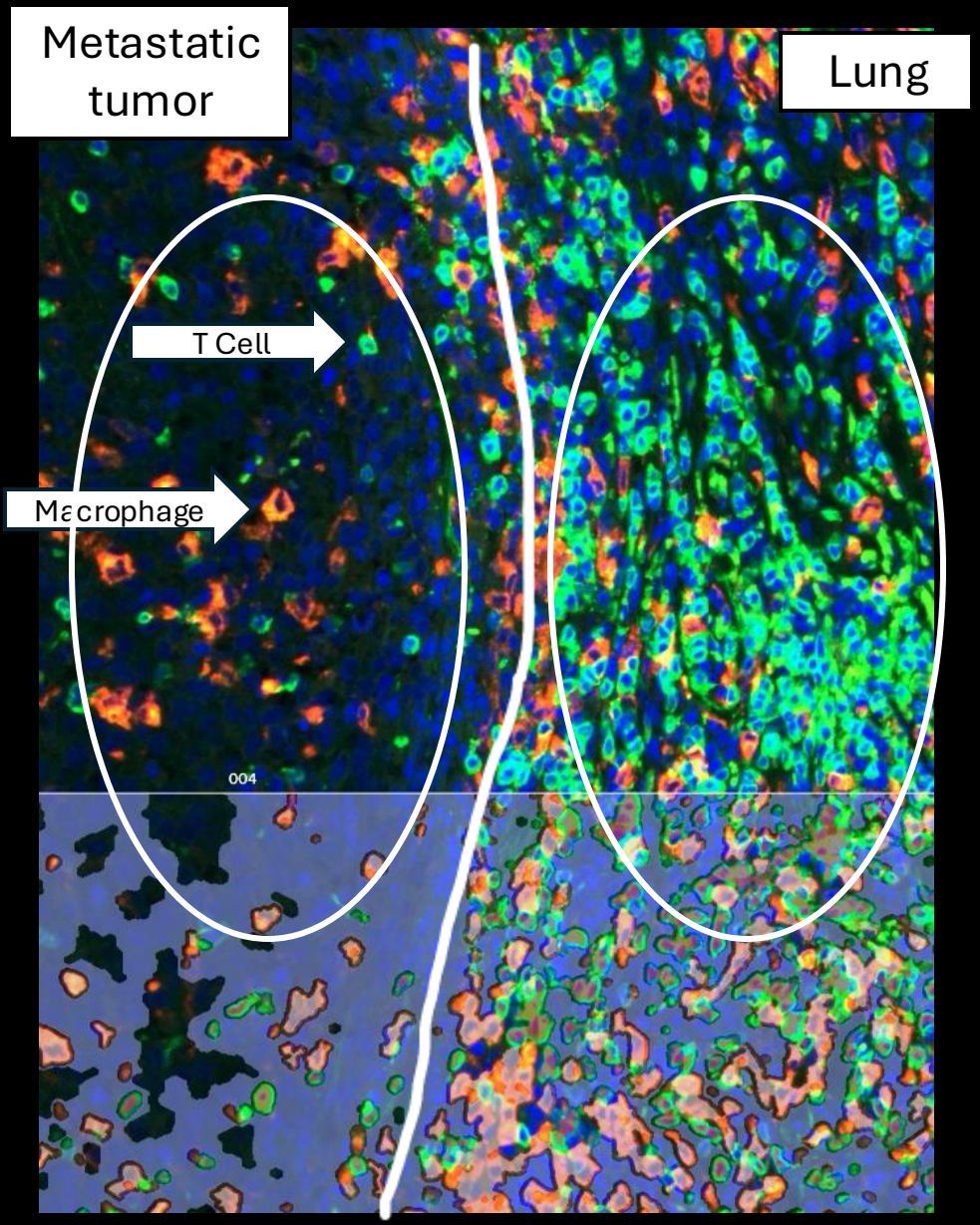
High MYC samples have depletion of functional T cell markers



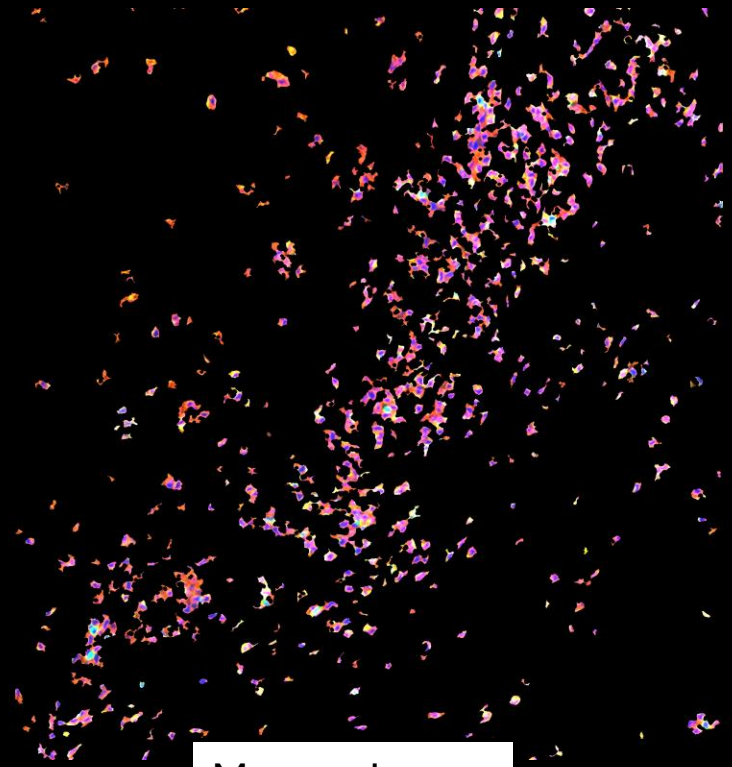
GeoMx Spatial Profiling



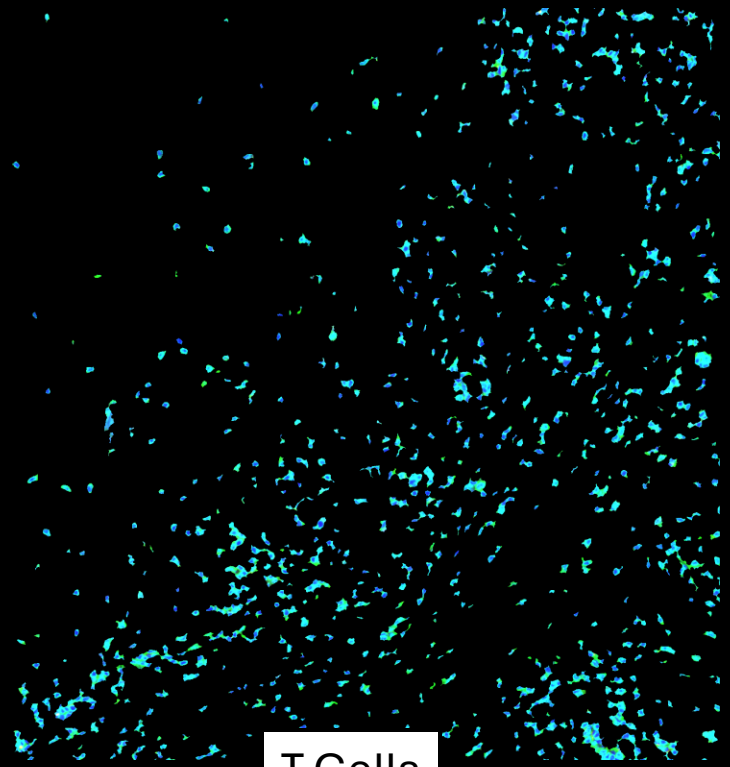

Metastatic tumor
003
004
Lung
008


Metastatic tumor
Lung
T Cell
Macrophage
004

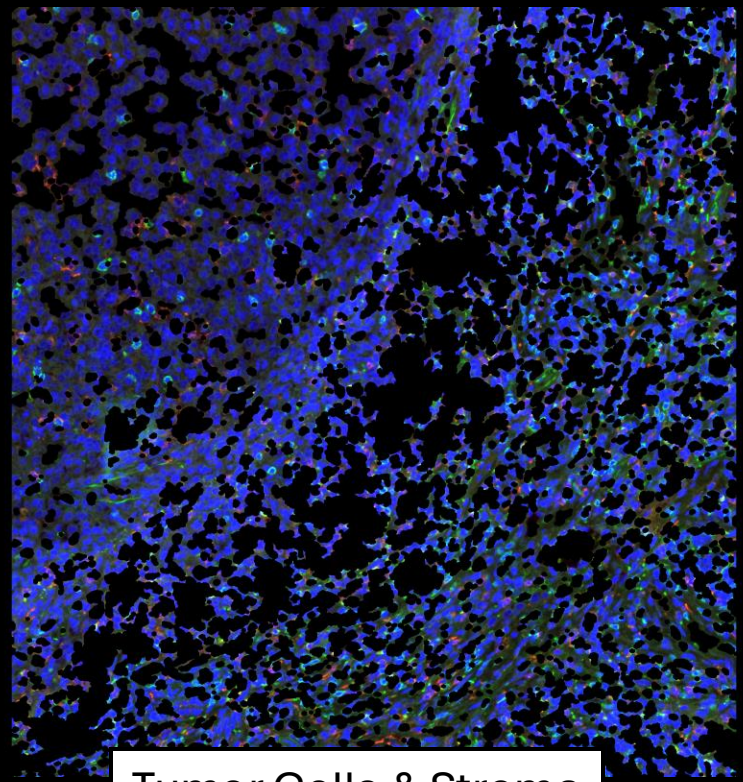
Count & capture unique transcriptional profile based on cell type



Macrophages

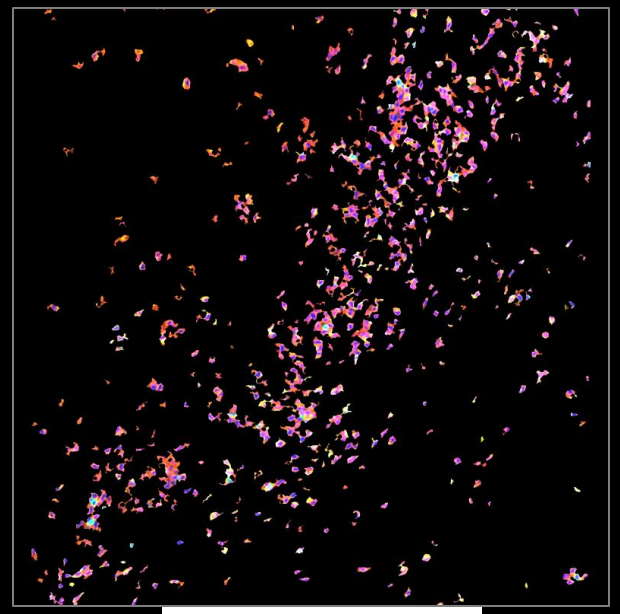


T Cells

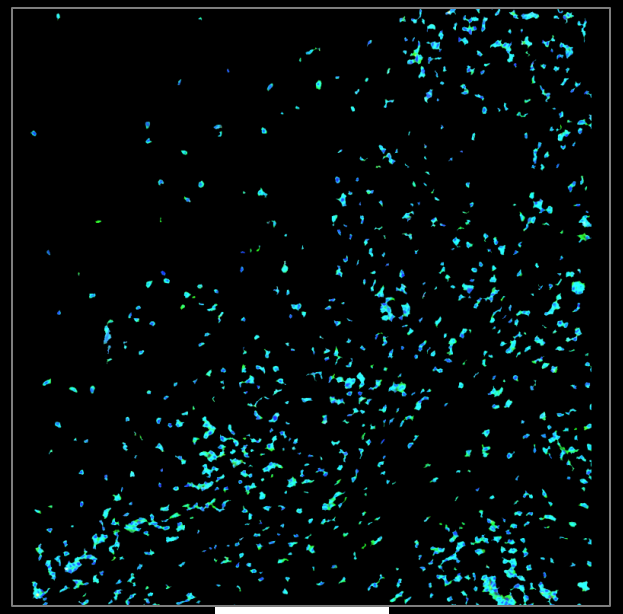


Tumor Cells & Stroma

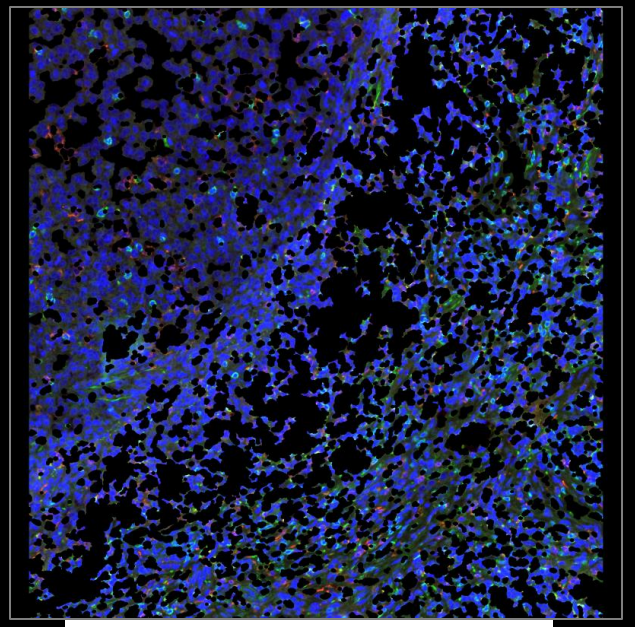
MYC Low



Macrophages

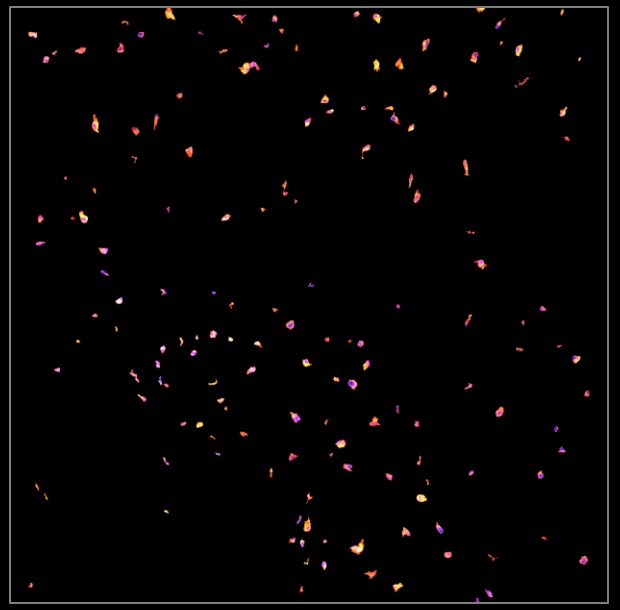


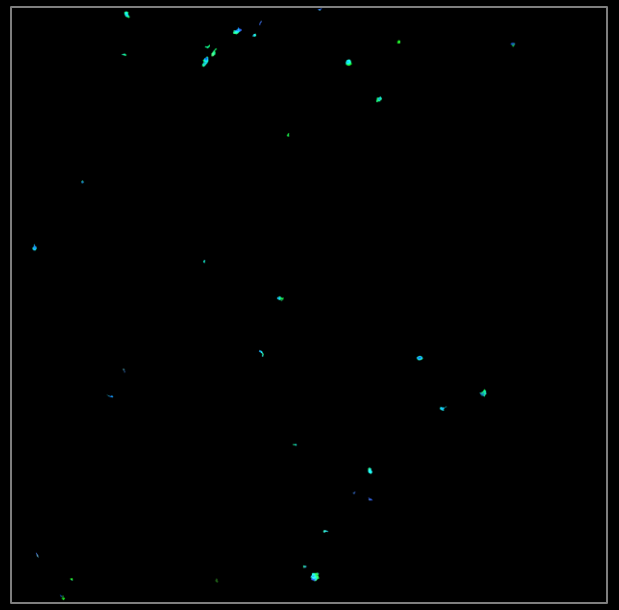
T Cells

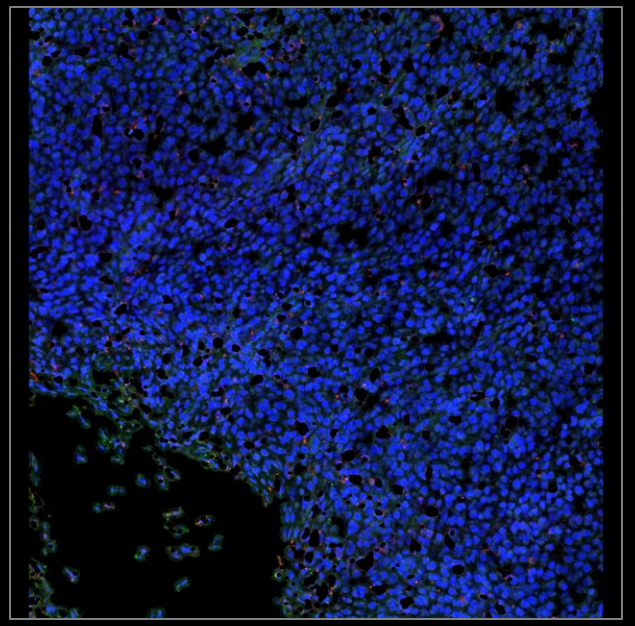


Tumor Cells & Stroma

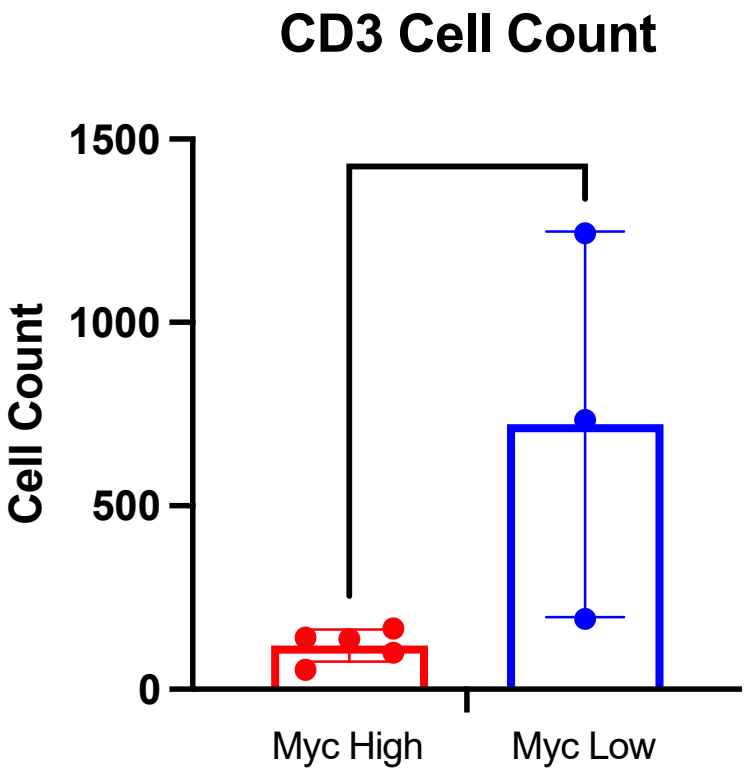
MYC High



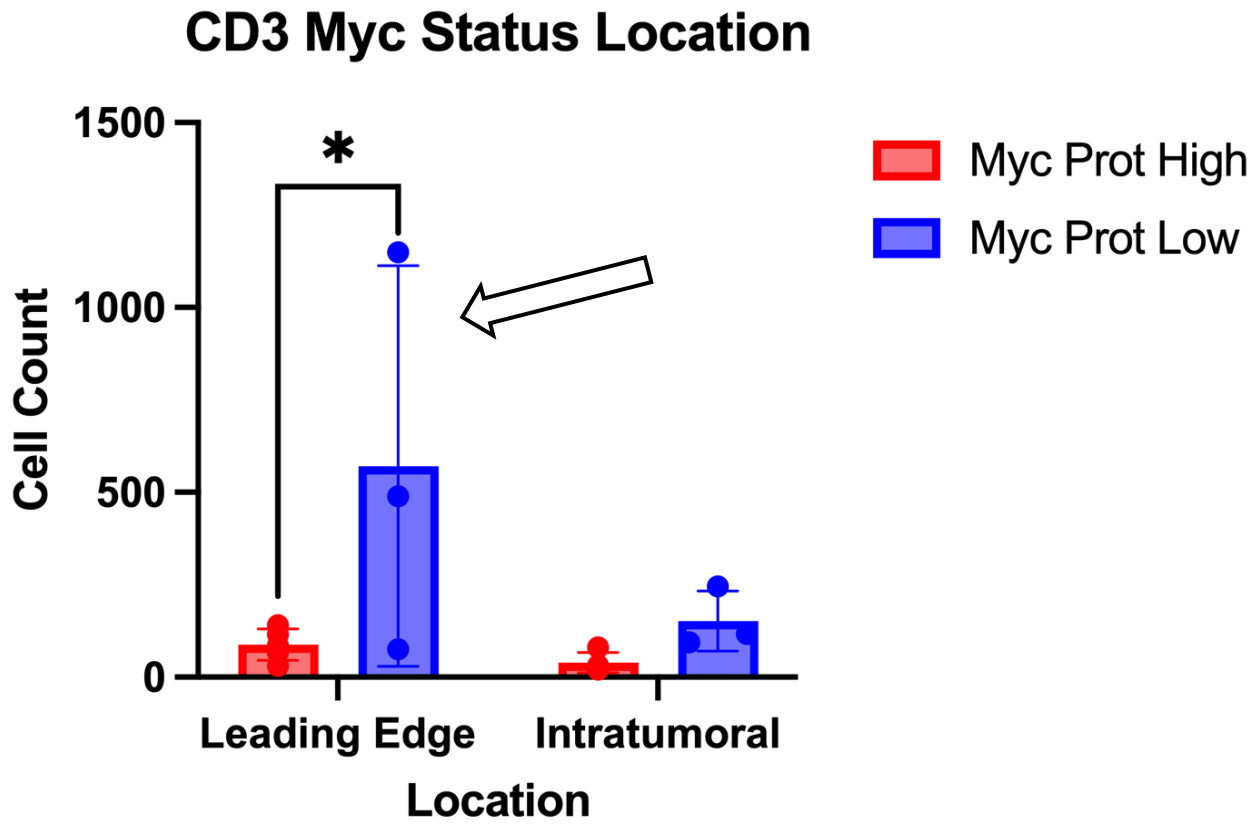


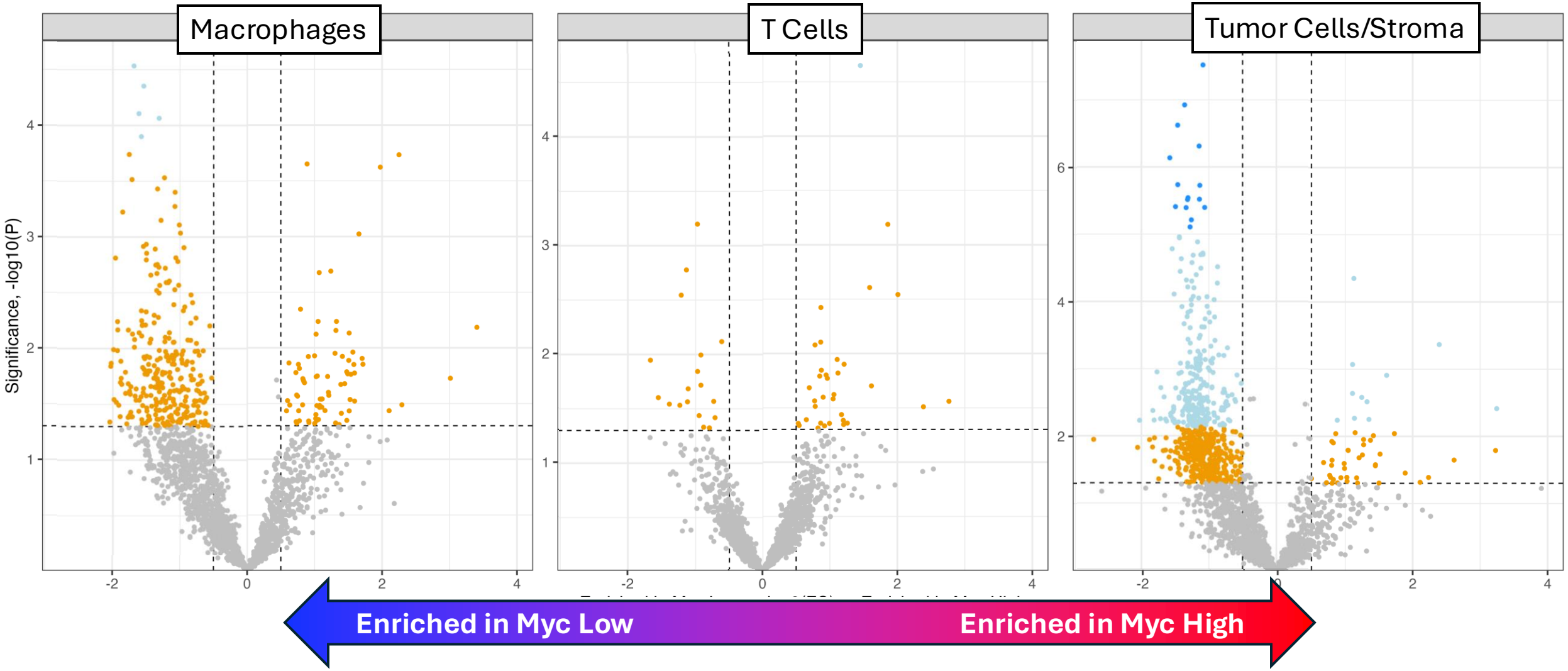


MYC high tumors have significantly lower CD3+ T cells

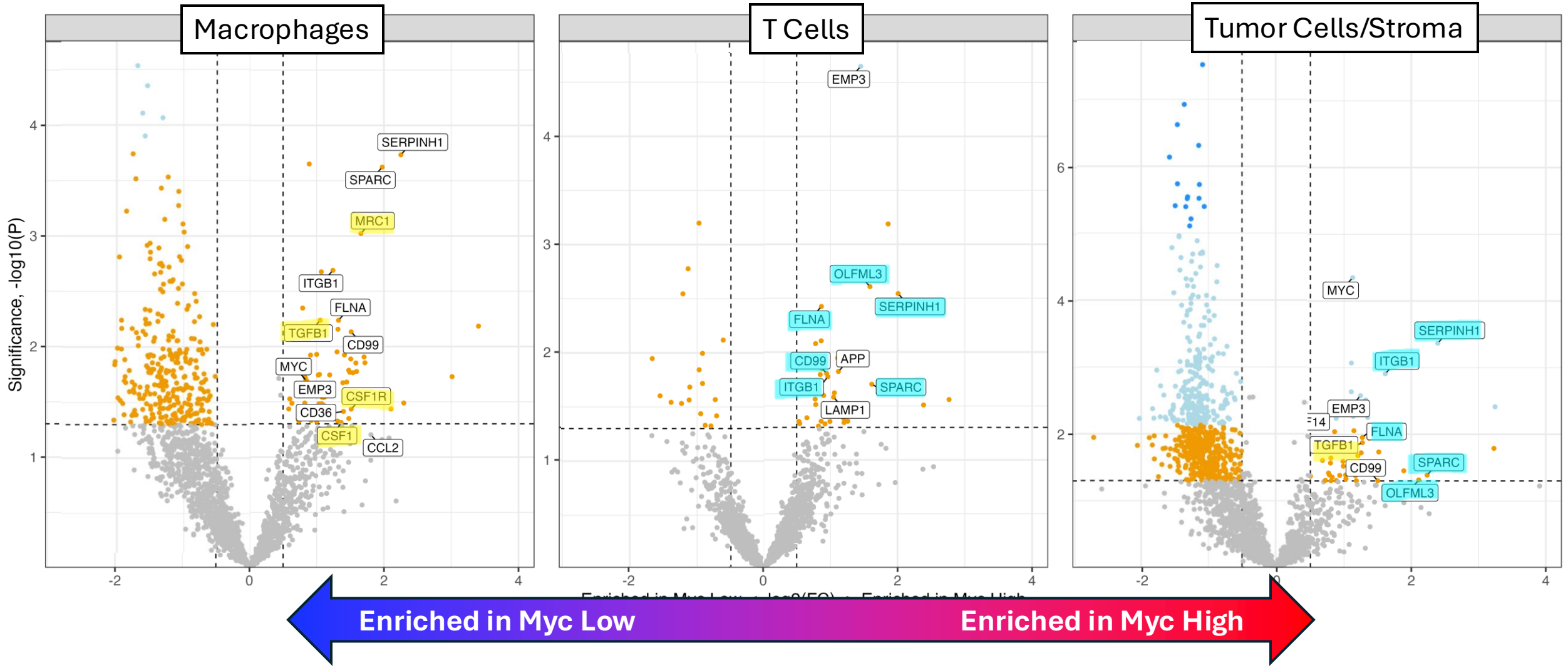


MYC high tumors have significantly lower CD3+ T cells **at the tumor-lung interface**

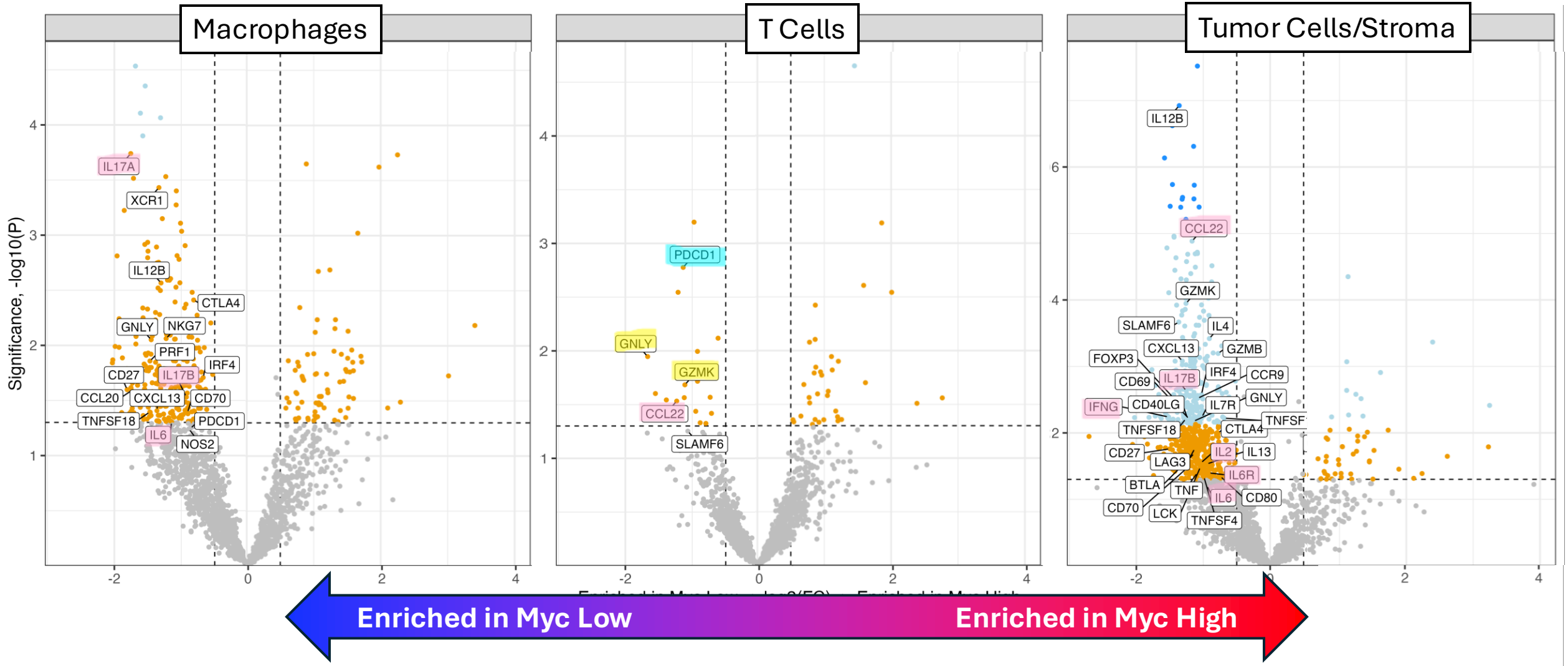



Macrophages
T Cells
Tumor Cells/Stroma
Significance, -log10(P)
Enriched in Myc Low
Enriched in Myc High

MYC high samples are enriched for tumor associated macrophages, extracellular matrix proteins, cell adhesion proteins, and TGFB1

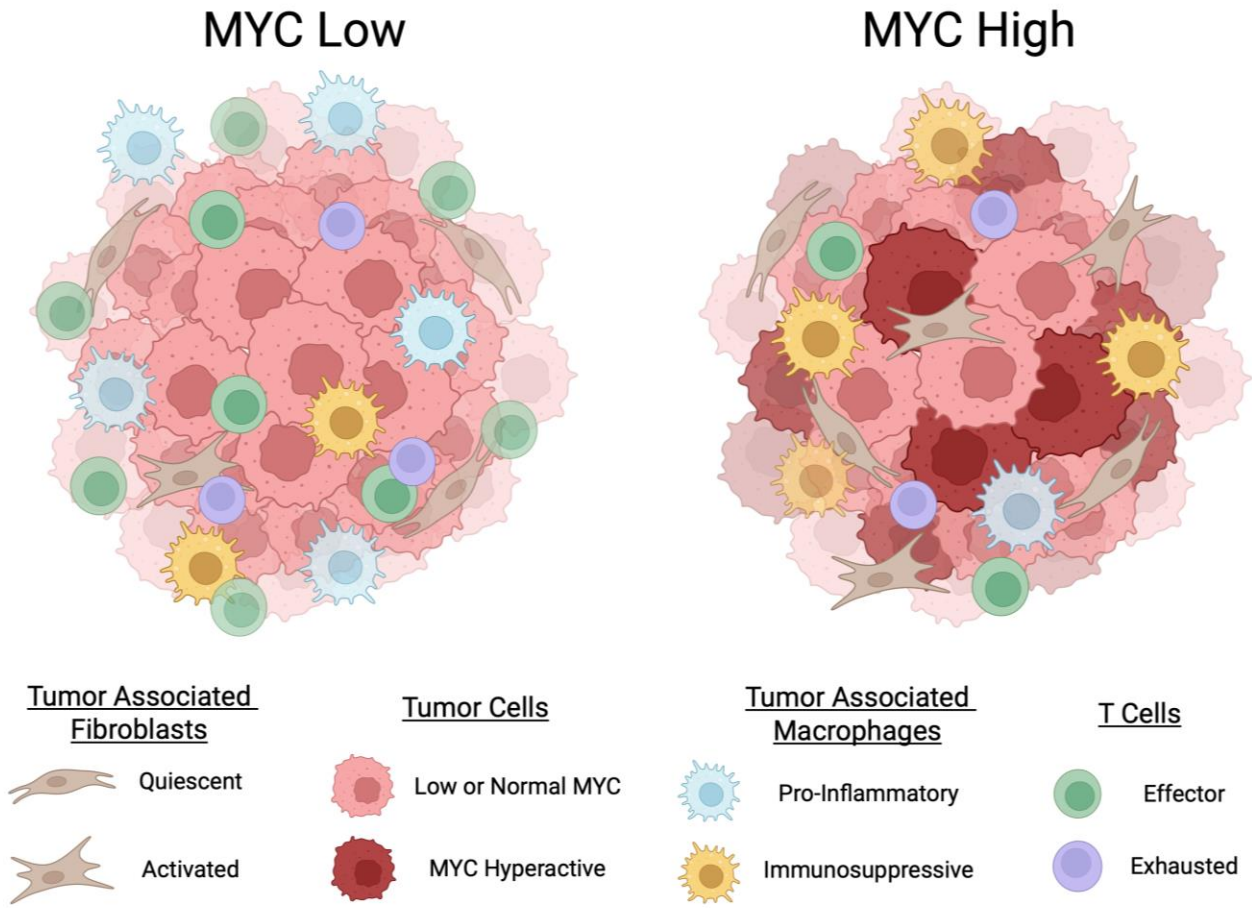


MYC high samples have **loss** of effector T cell signals, immune checkpoints, and pro-inflammatory molecules



Conclusions

- MYC overexpression in canine metastatic OS is not genomically driven
- High MYC protein samples are enriched for immunosuppressive TAMs
- High MYC protein samples have lower T cell infiltrates at the tumor margins and transcriptional loss of effector function
- High MYC samples have loss of immune checkpoints
  - Contrasts MYC immunosuppression mechanisms in other cancers
- MYC protein status may be beneficial as an immunotherapy prognostic indicator or target



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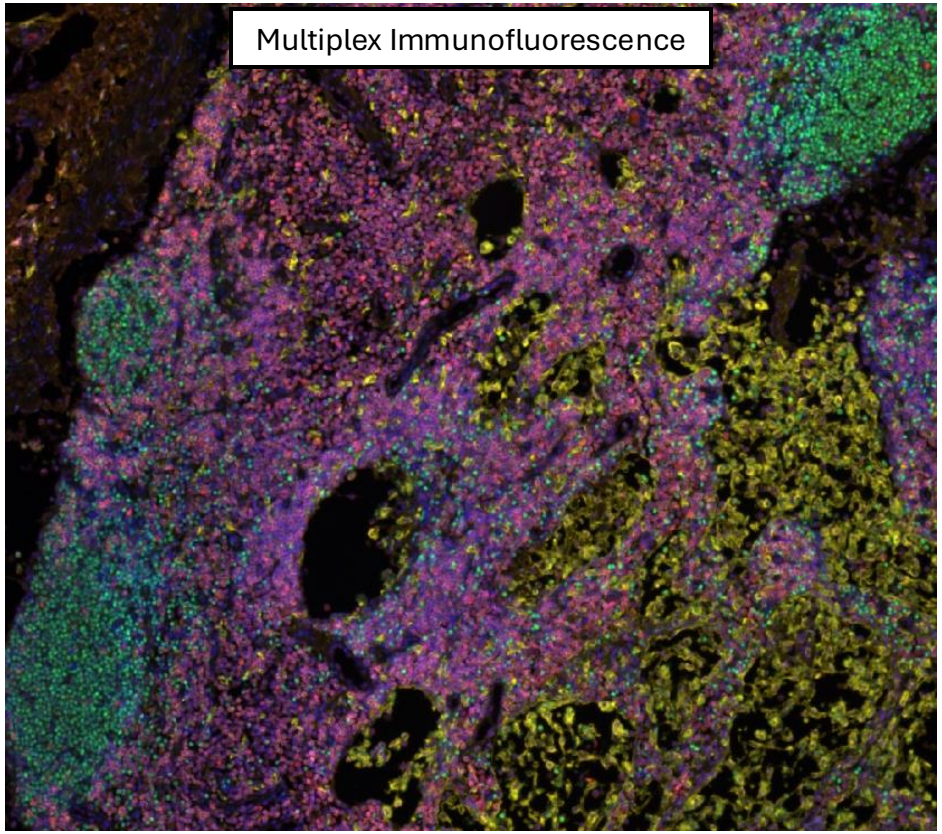
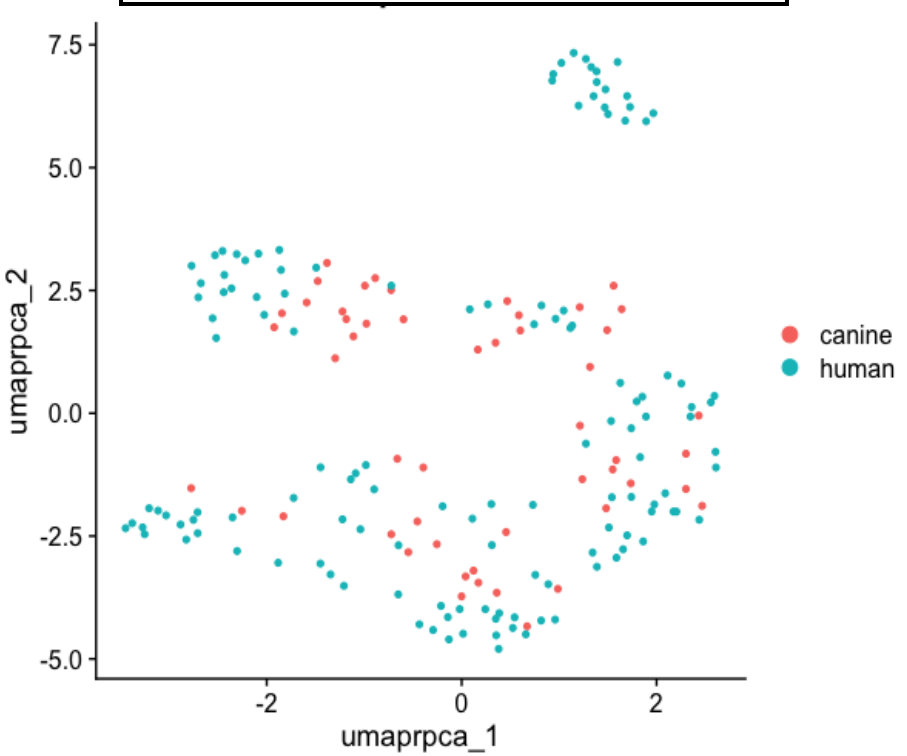
Work In Progress…

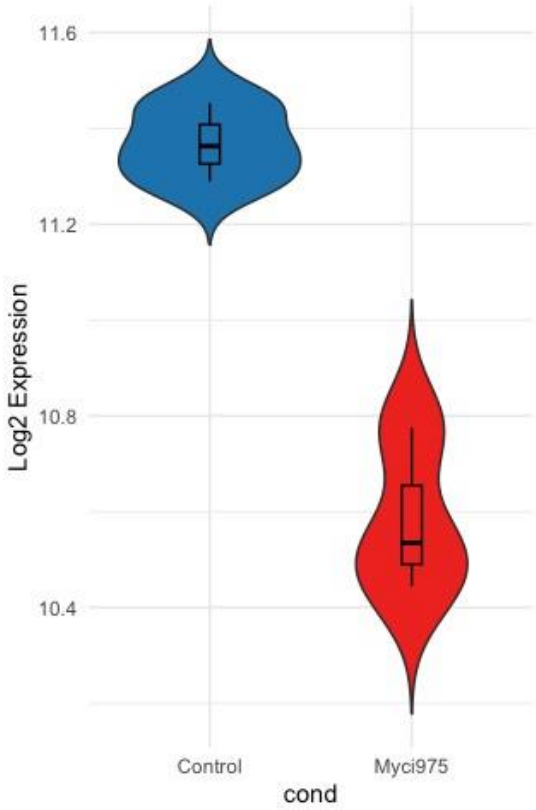
Multiplex Immunofluorescence



GeoMX Canine & Human Integration



Myc Expression – 143b



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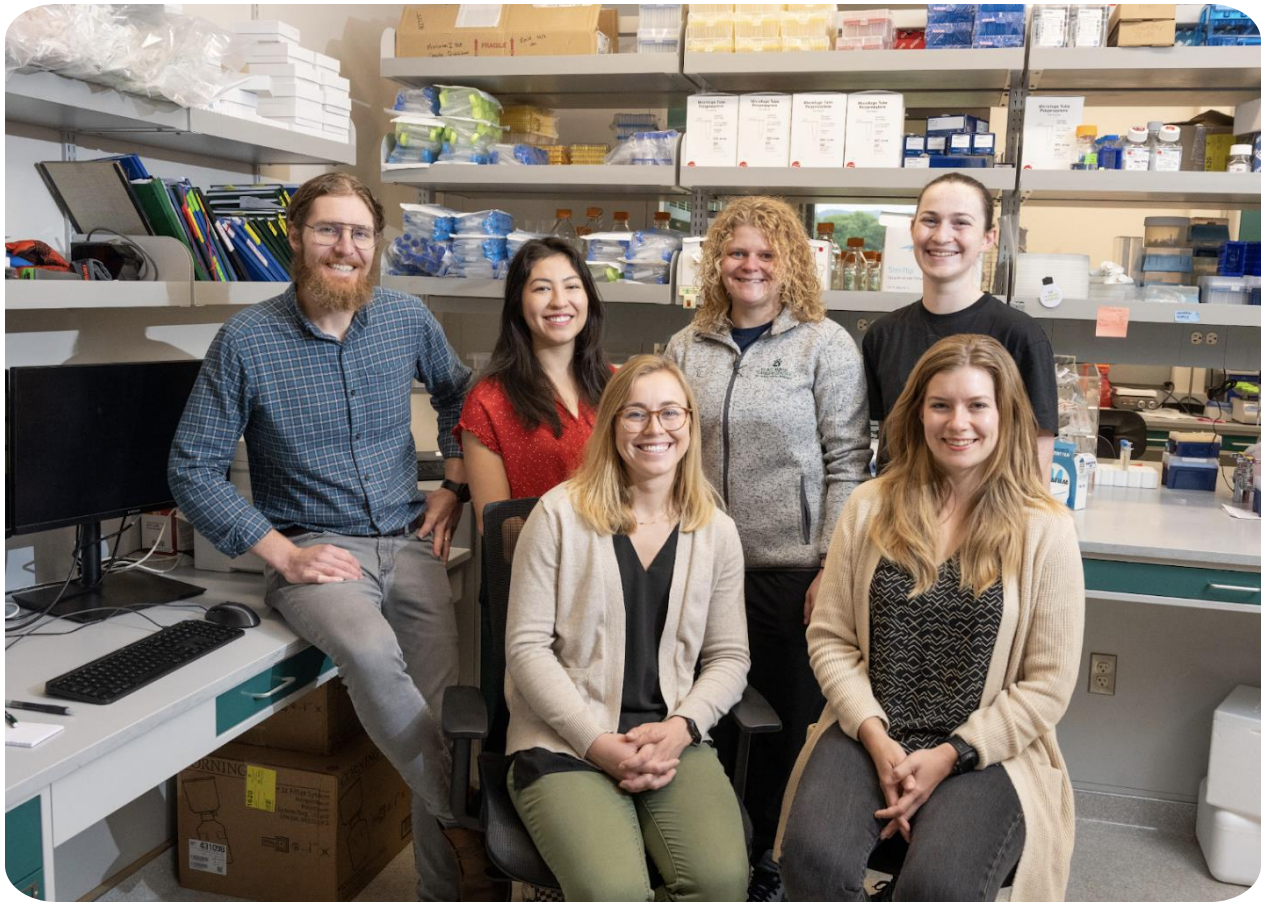
Acknowledgements



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💛 Our canine patients & their families

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