

**Bofei Wang<sup>1\*</sup>, Patrick K Reville<sup>1\*</sup>, Yousuf Yassouf<sup>1</sup>, Fatima Z Jelloul<sup>1</sup>, Poonam N Desai<sup>1,2</sup>, Zhe Wang<sup>1</sup>, Pamella Borges<sup>1,3</sup>, Christopher Ly<sup>1</sup>, Ivo Veletic<sup>1</sup>, Enes Dasdemir<sup>1,3</sup>, Jared K. Burks<sup>1</sup>, Guilin Tang<sup>1</sup>, Shengnan Guo<sup>4</sup>, Araceli Isabella Garza<sup>1</sup>, Cedric Nasnas<sup>1</sup>, Nicole R Vaughn<sup>1</sup>, Natalia Baran<sup>1</sup>, Qing Deng<sup>1</sup>, Jairo Matthews<sup>1</sup>, Preethi H Gunaratne<sup>3</sup>, Dinler A Antunes<sup>3</sup>, Suhendan Ekmekcioglu<sup>1</sup>, Koji Sasaki<sup>1</sup>, Miriam Garcia<sup>1</sup>, Branko Cuglievan<sup>1</sup>, Dapeng Hao<sup>4</sup>, Naval Daver<sup>1</sup>, Michael R Green<sup>1</sup>, Marina Konopleva<sup>1</sup>, Andrew Futreal<sup>1</sup>, Sean M Post<sup>1</sup>, Hussein A Abbas<sup>1</sup>** (\*co-first)

<sup>1</sup>The University of Texas MD Anderson Cancer Center, Houston, TX, USA. <sup>2</sup>The University of Texas Health Science Center, Houston, TX, USA.

**<sup>3</sup>University of Houston, Houston, TX, USA. <sup>4</sup>Harbin Medical University, Harbin, China.**

# Background

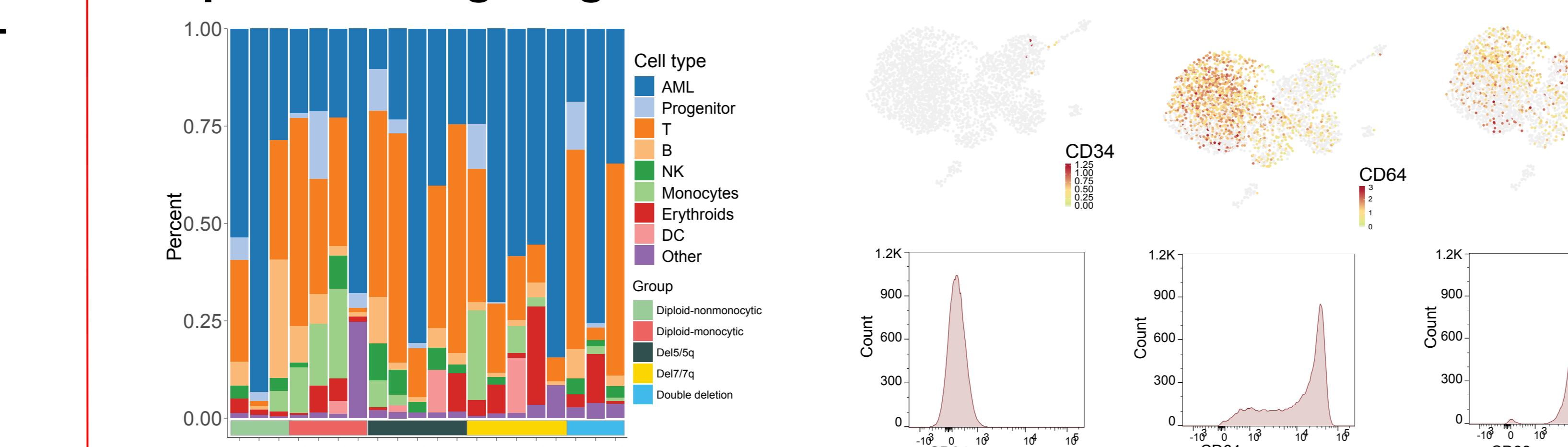
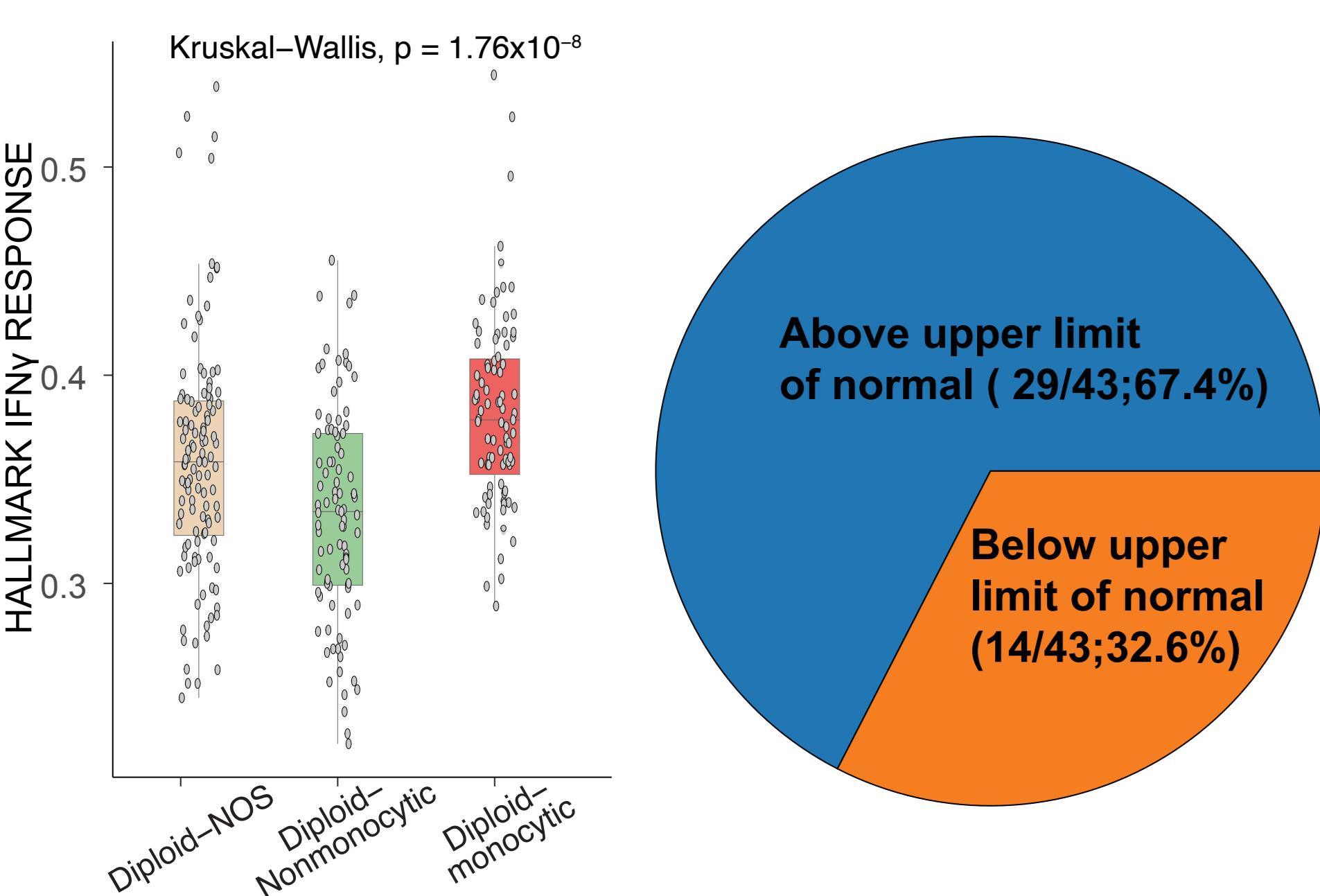
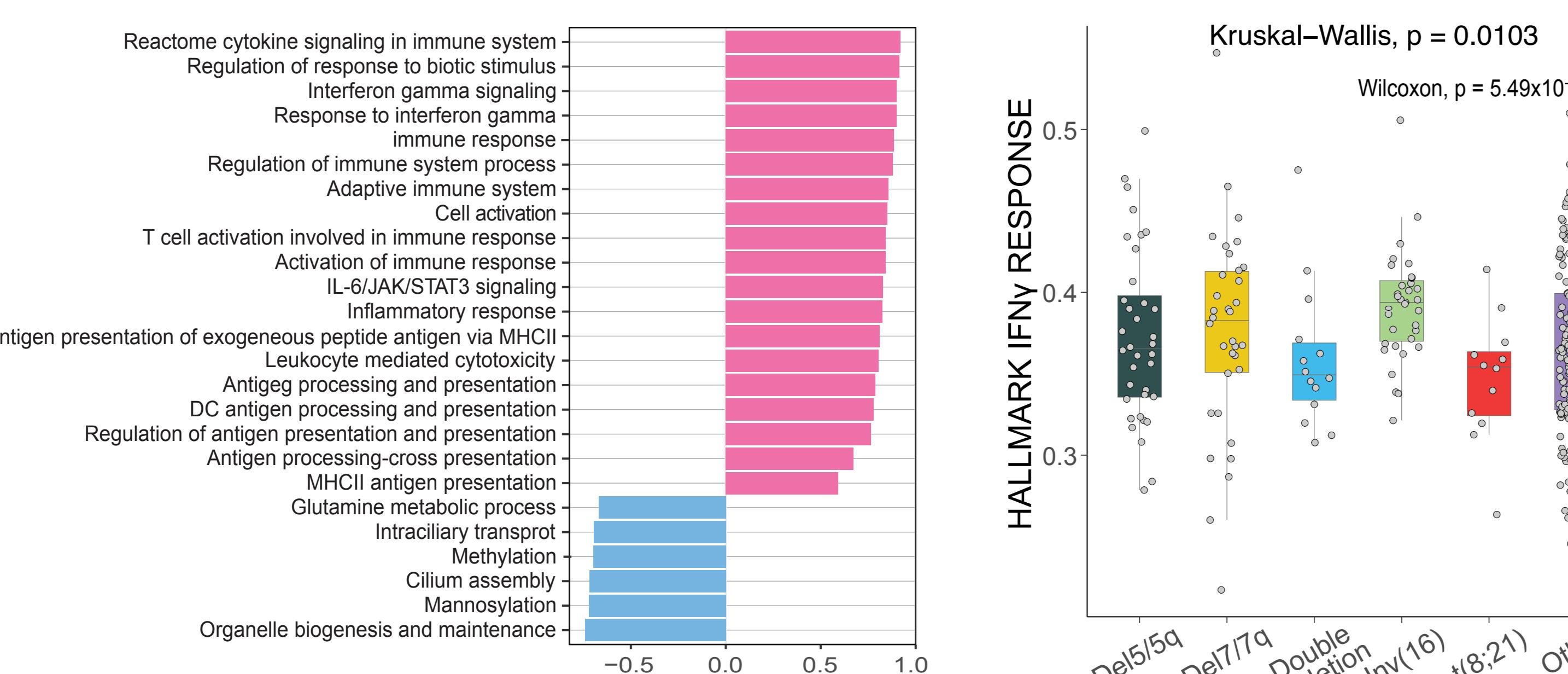
Interferon gamma (IFN $\gamma$ ) is a critical cytokine known for its diverse roles in immune regulation, inflammation, and tumor surveillance. Studies have reported the dichotomous nature of IFN $\gamma$  signaling in both the pathogenesis of cancer and immunotherapy response. However, its complex interplay with acute myeloid leukemia (AML) remains insufficiently understood. Also, The mechanisms of resistance to venetoclax are not fully understood but monocytic subclones are suggested to have inherent resistance to venetoclax.

## Methods

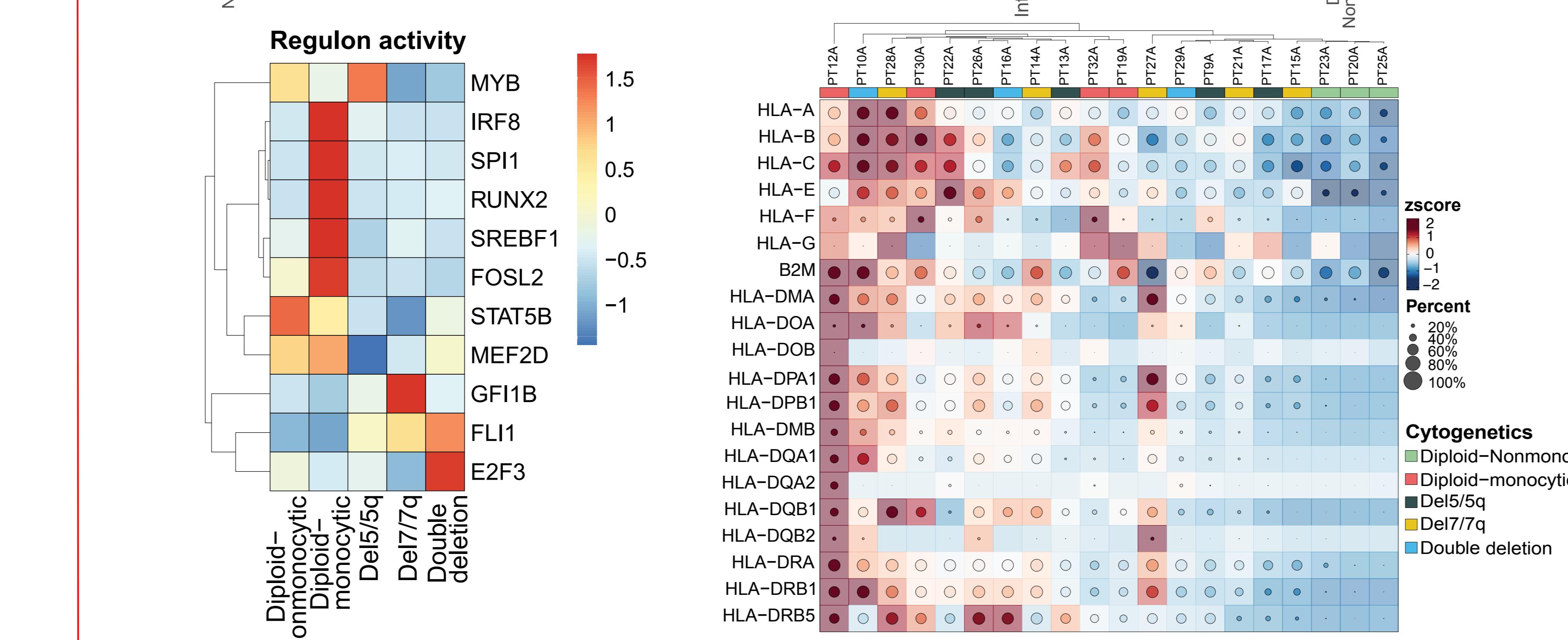
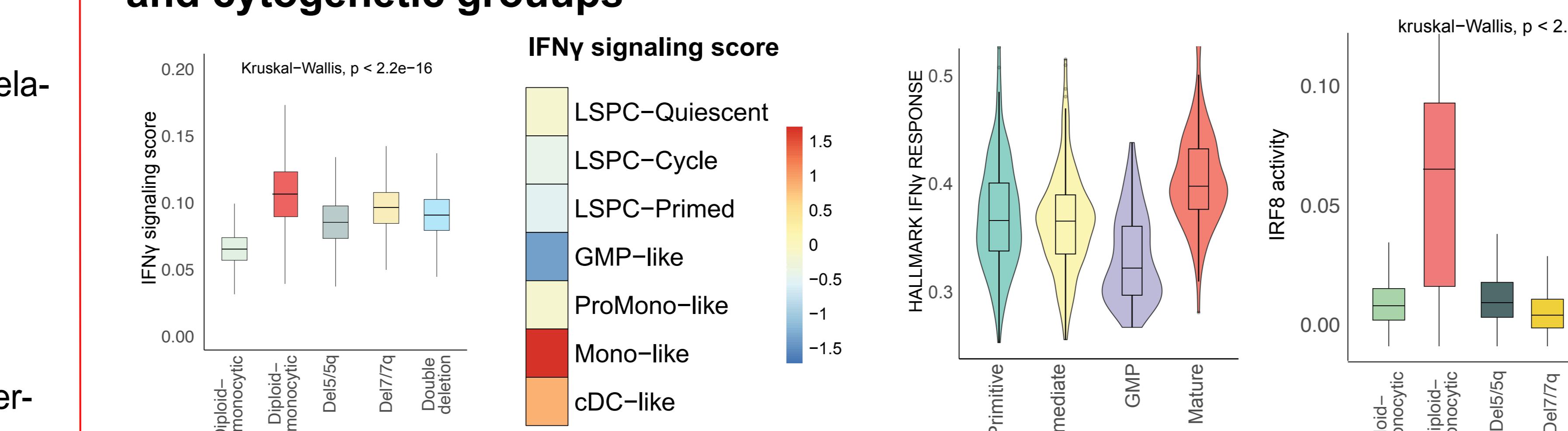
- Three independent RNA-seq datasets were integrated to disentangle the IFNy response signaling in AML
  - Single cell RNA sequencing (scRNA) on 20 newly diagnosed AML patients to discern relative contribution of cells and cellular communications for IFNy signaling
  - AML blasts and T cells co-culture assay to assess the capacity of AML cells to directly induce INF $\gamma$  secretion. Treatment of AML blasts with Venetoclax validate the role of IFNy signaling in AML cell survival and drug resistance
  - The NanoString GeoMX DSP whole transcriptome assay was used to spatially characterize

## Results

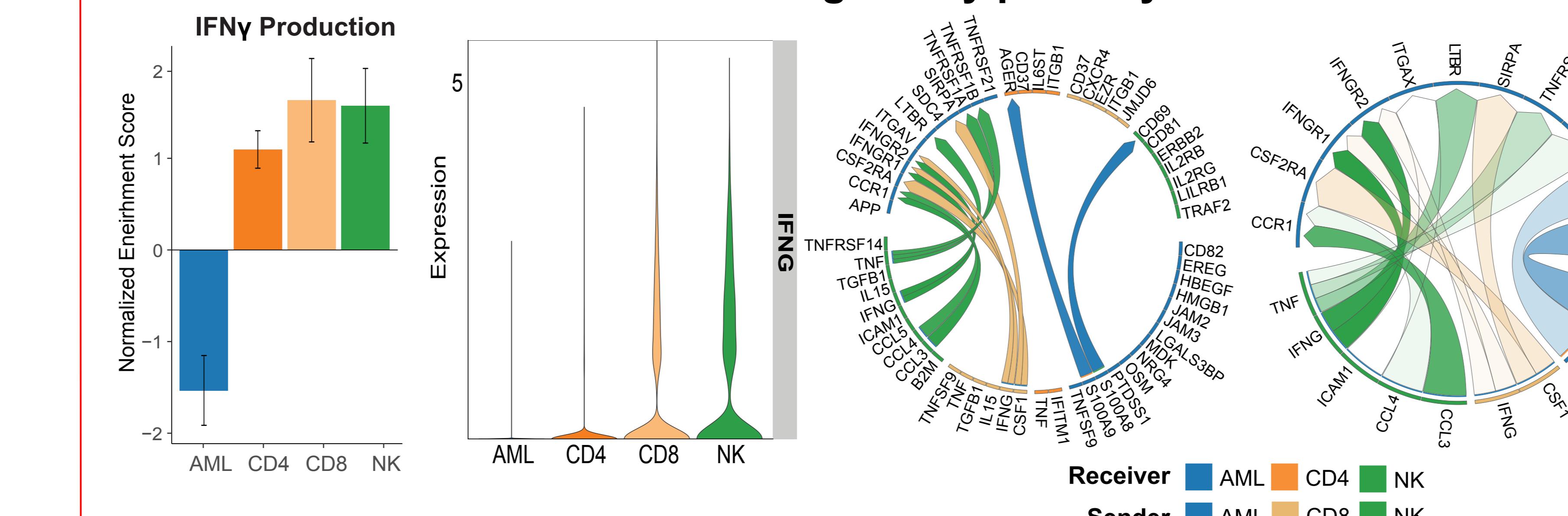
# Differential IFN $\gamma$ activity in distinct subgroups of AML patients



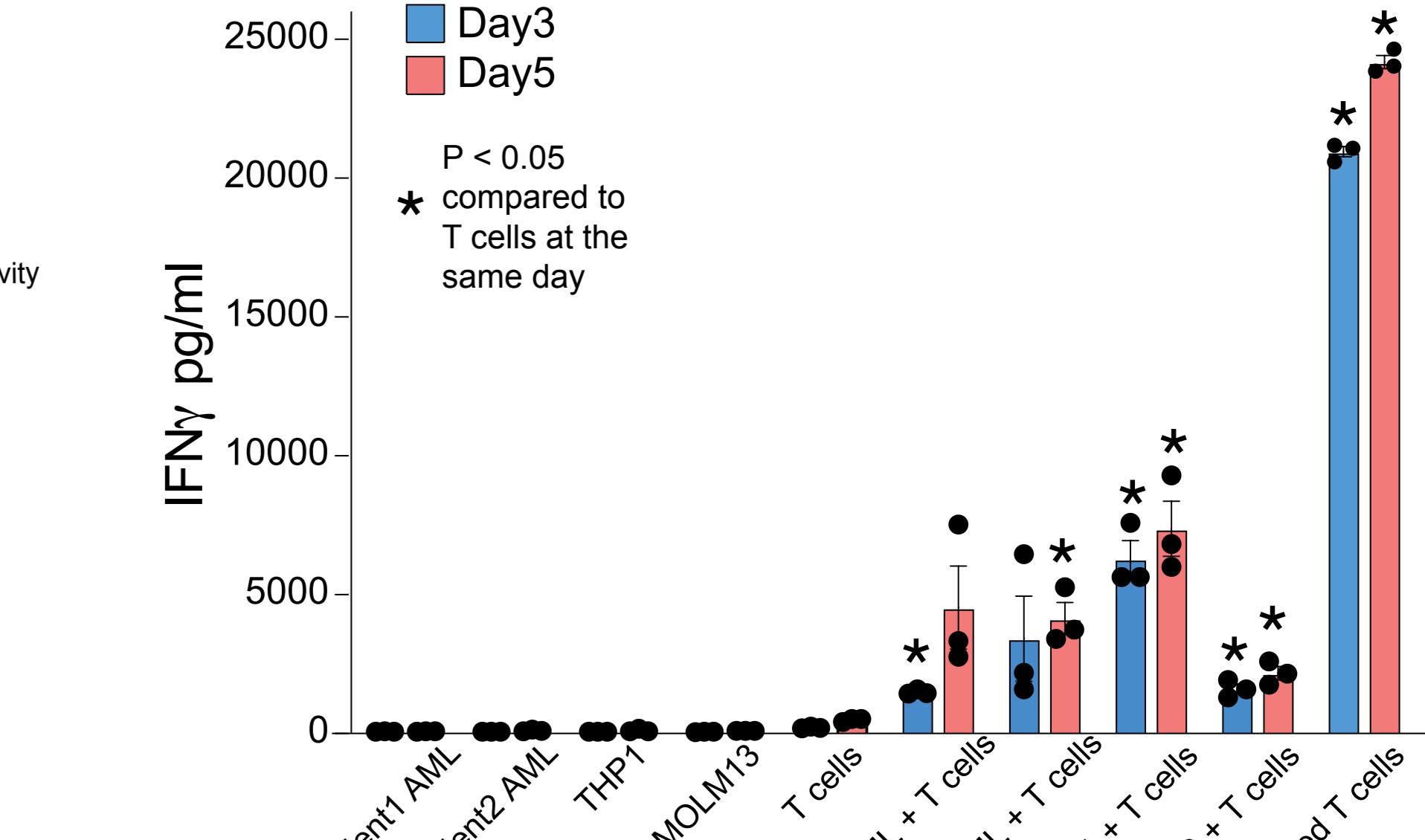
**IFNy signaling activation in AML blasts is dependent on AML hierarchy and cytogenetic groups**



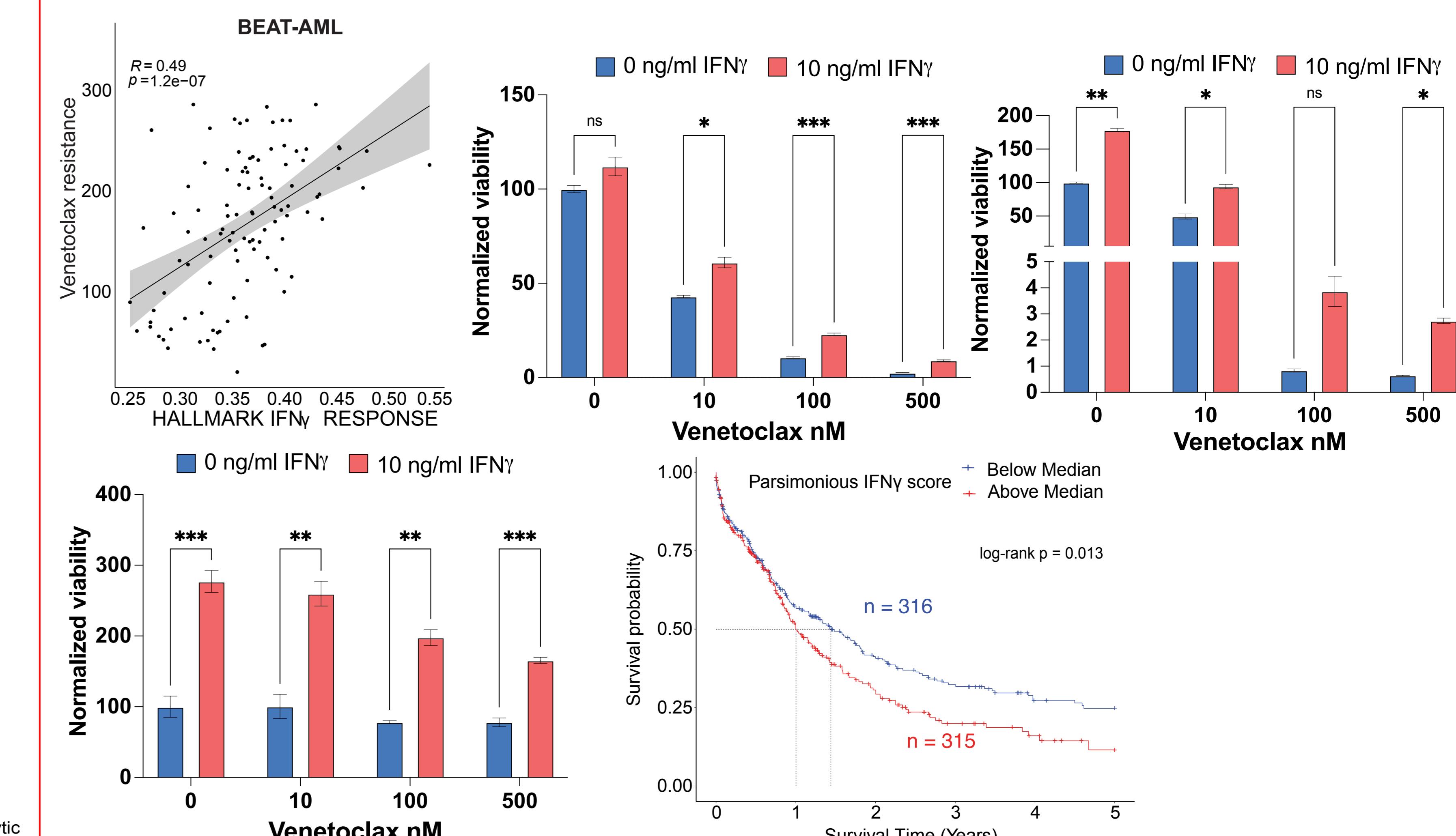
# High IFNy pathway activation in AML cells is correlated with T cell inflammatory microenvironment and distinct regulatory pathway activation



# Ex vivo T-AML cell co-culture stimulates IFNy production



# IFNy signaling confers venetoclax resistance



## Conclusions

Characterization of inflammation in AML using independent bulk and scRNA profiling led to the identification of novel drug targets and mechanisms of resistance to targeted therapy. We identified monocytic AML as having a unique microenvironment characterized by high IFN $\gamma$  signaling in AML cells and immunosuppressive features. IFN $\gamma$  signaling scores correlated strongly with venetoclax resistance. A parsimonious IFN $\gamma$  gene signature demonstrated robust prognostic value.

# References

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# Contact information

Hussein A. Abbas, MD, PhD. EMAIL: habbas@mdanderson.org