Single-cell RNA sequencing reveals that imatinib alters tumor-associated macrophages in GIST

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Disclosure

- No financial relationships to disclose

GIST and immunotherapy

- Most common human sarcoma
  - Mostly gastric, small bowel
- Imatinib: first line TKI therapy
  - Rarely curative
  - Resistance → progression
- Immunotherapy in GIST is ineffective

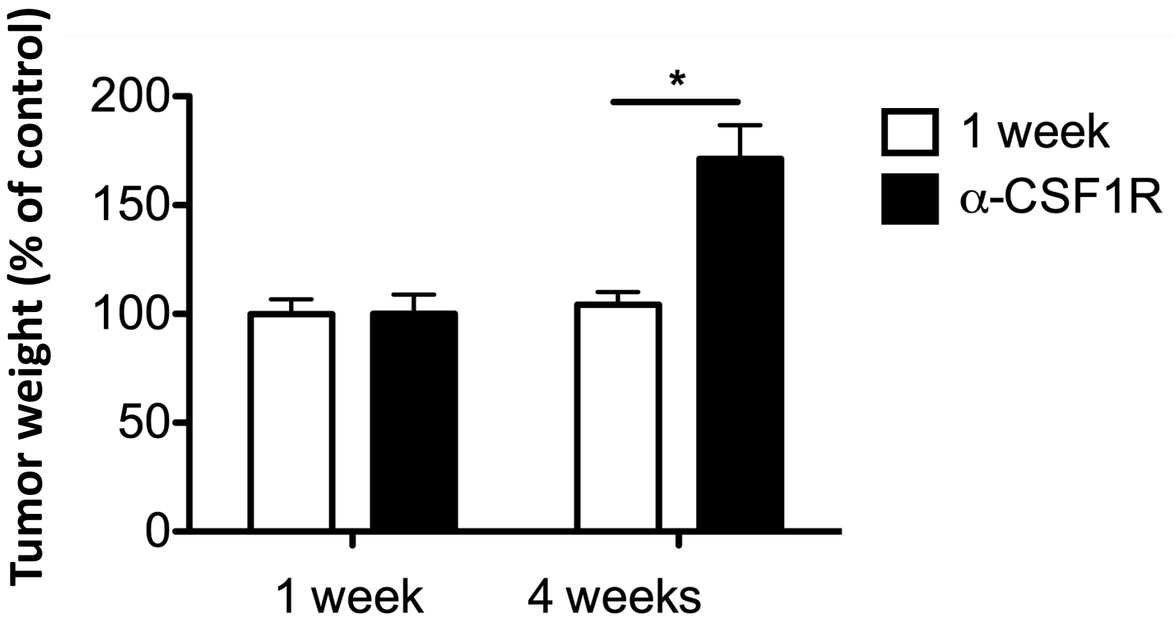
Immunotherapy Trials in GIST

Agents	Summary
Dasatinib + Ipilimumab	Phase I/II Advanced GIST Median PFS < 6 mo
Pembrolizumab + Cyclophosphamide	
Nivolumab ± Ipilimumab	
Imatinib + Spartalizumab (anti-PD-1)	

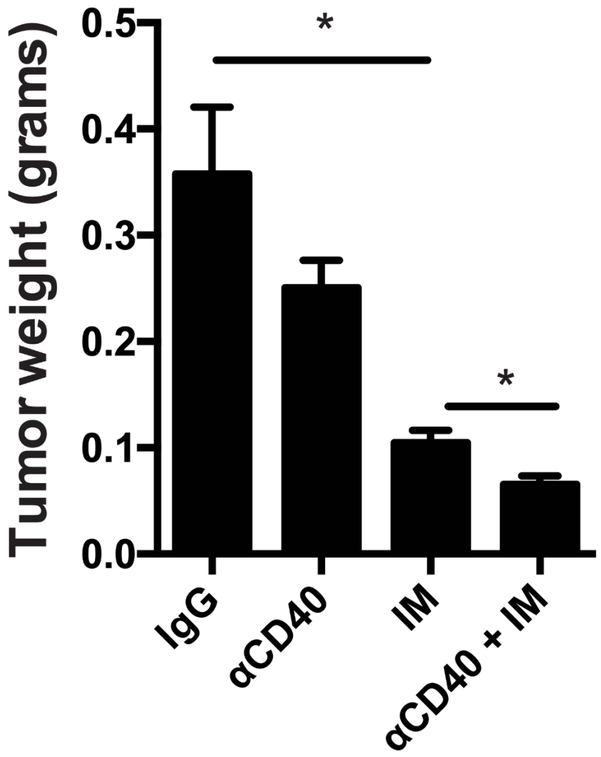
D'Angelo, M. *Clin Can Res.* (2017)
Toulmonde, M. *JAMA Onc.* (2018)
Singh, A.S. *Clin Can Res.* (2022)
Kim, H.D. *Clin Can Res. (*2024)

Tumor-associated macrophages (TAMs) are anti-tumoral in GIST

TAM depletion increases tumor weight



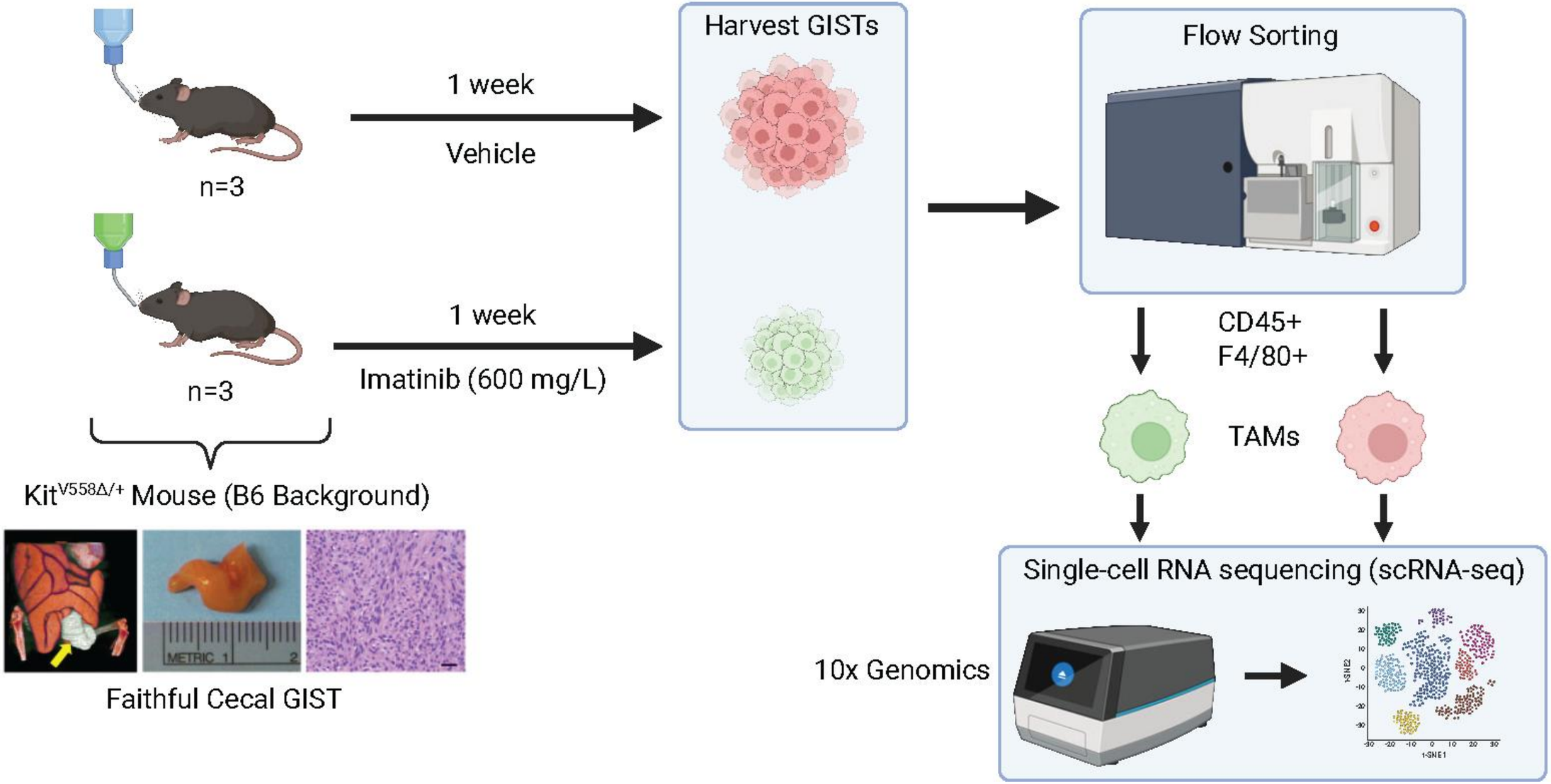
CD40 agonism augments imatinib therapy



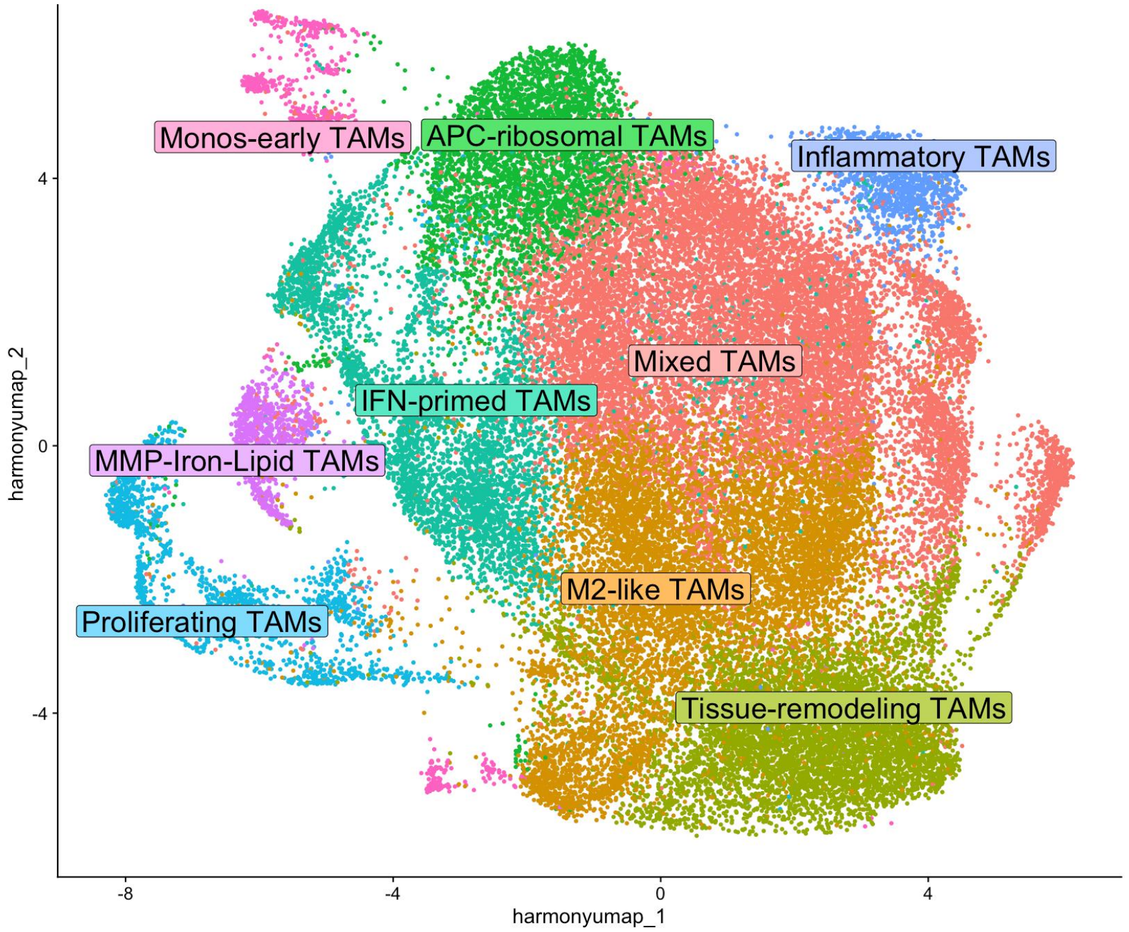
How?

Cavnar, M. *J Exp Med* (2013)
Zhang, J. *Cancer Imm Res* (2018)

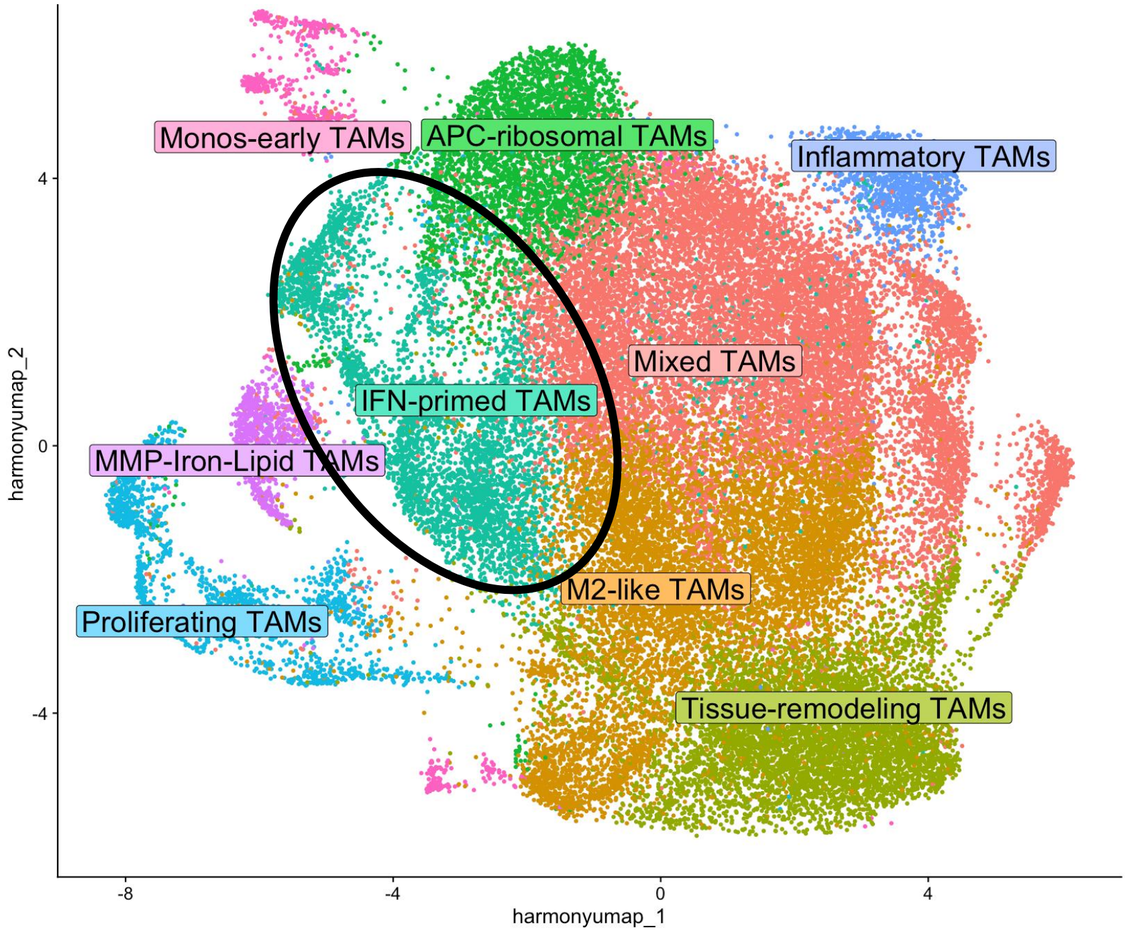
Methods


n=3
1 week
Vehicle
n=3
1 week
Imatinib (600 mg/L)
Kit$^{V558\Delta/+}$ Mouse (B6 Background)
Faithful Cecal GIST
Harvest GISTs
Flow Sorting
CD45+
F4/80+
TAMs
Single-cell RNA sequencing (scRNA-seq)
10x Genomics
tSNE2
tSNE1

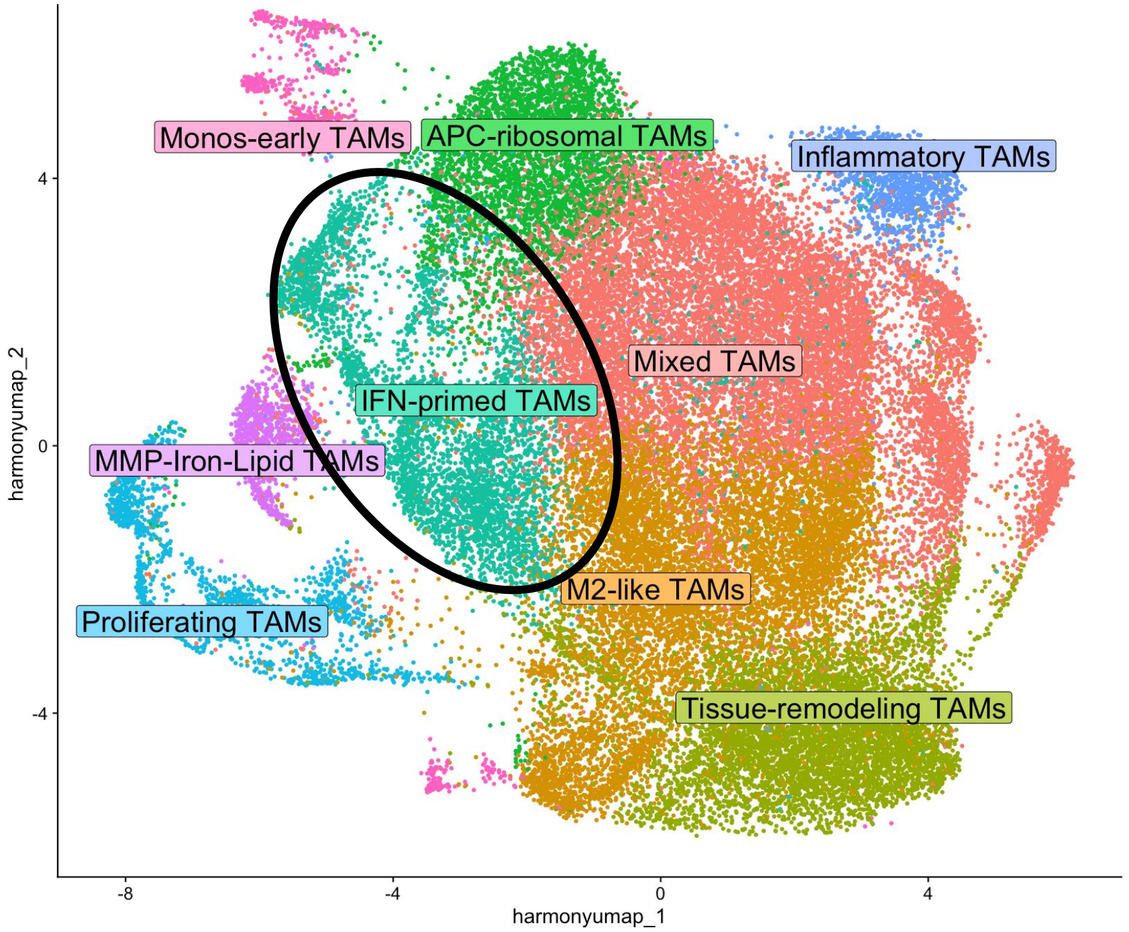
UMAP of GIST TAMs



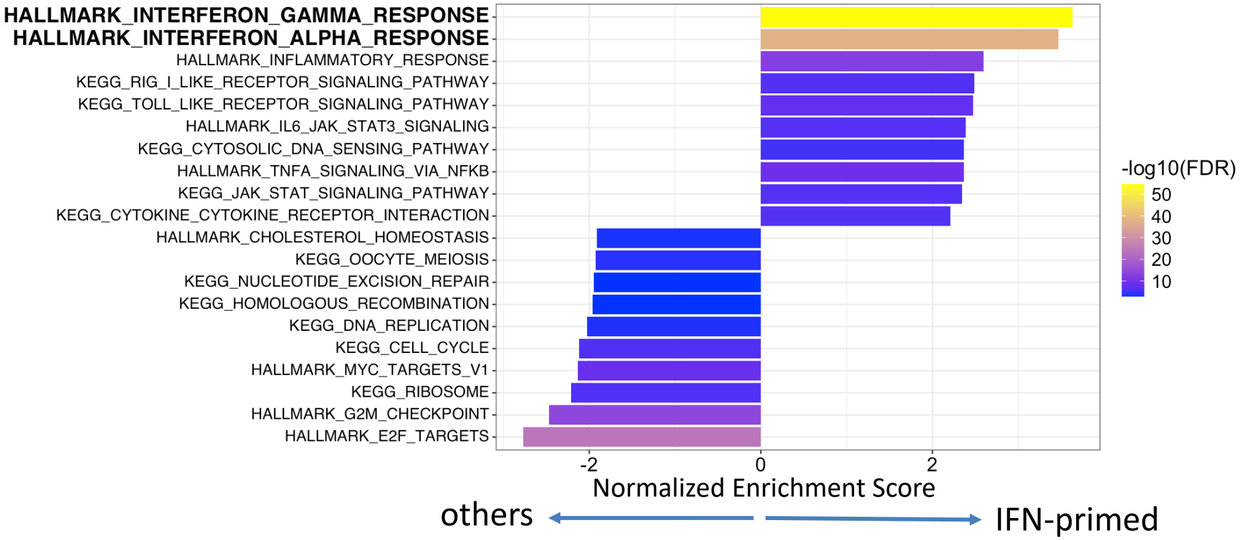
Interferon-primed TAMs



Interferon-primed TAMs

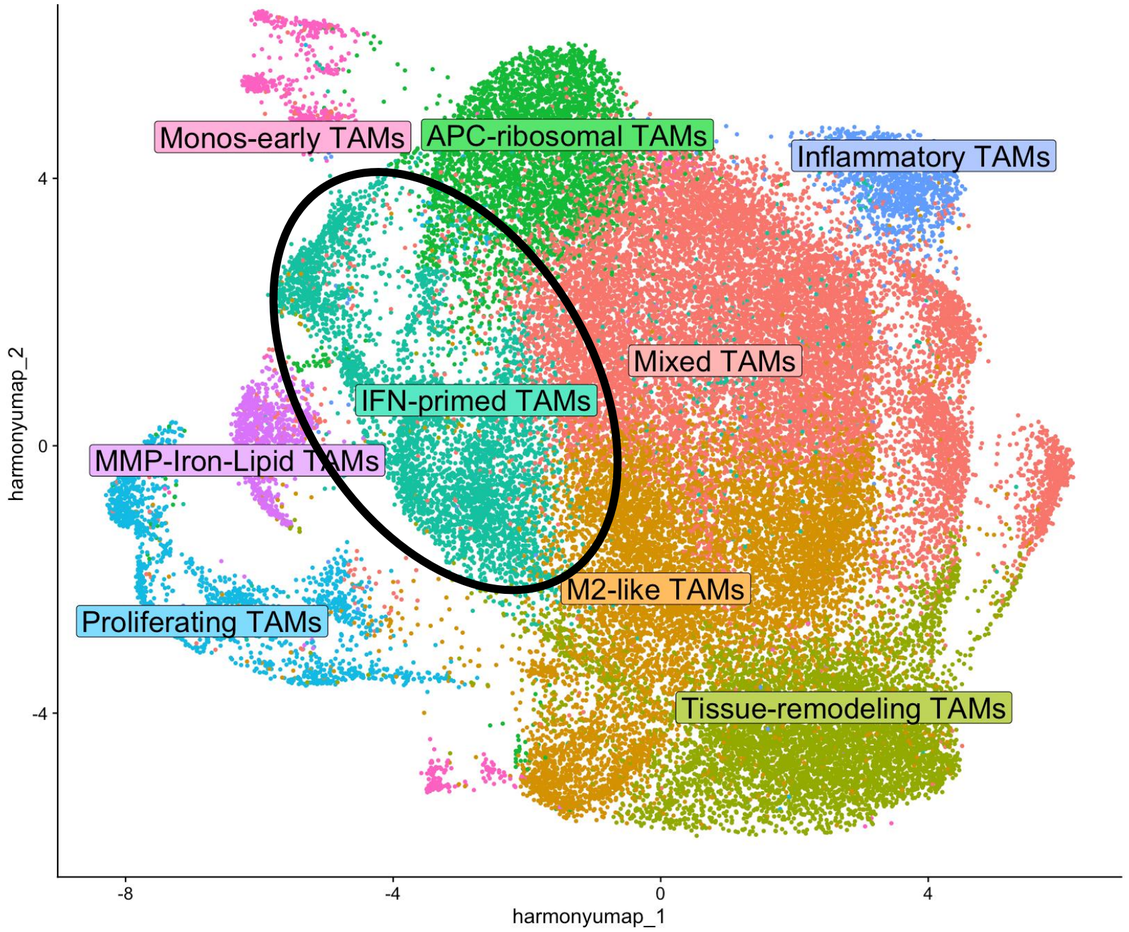


IFN-primed TAMs functionally enrich for IFN response



others ← → IFN-primed

Interferon-primed TAMs



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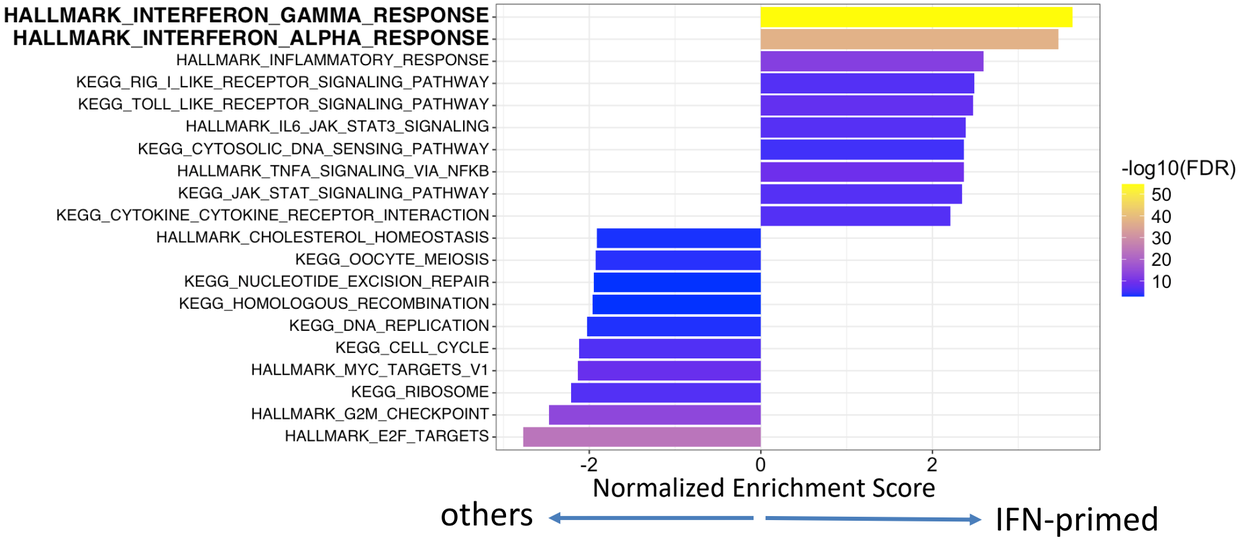
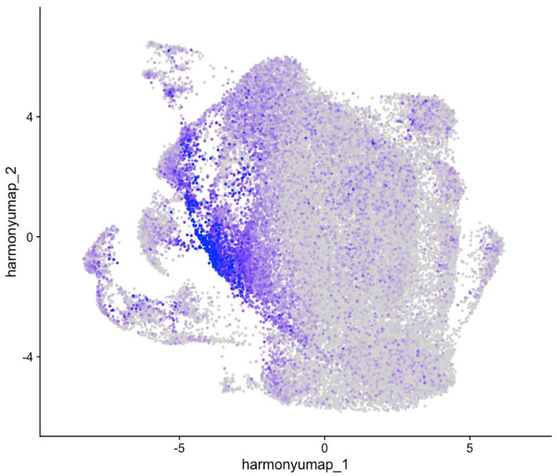
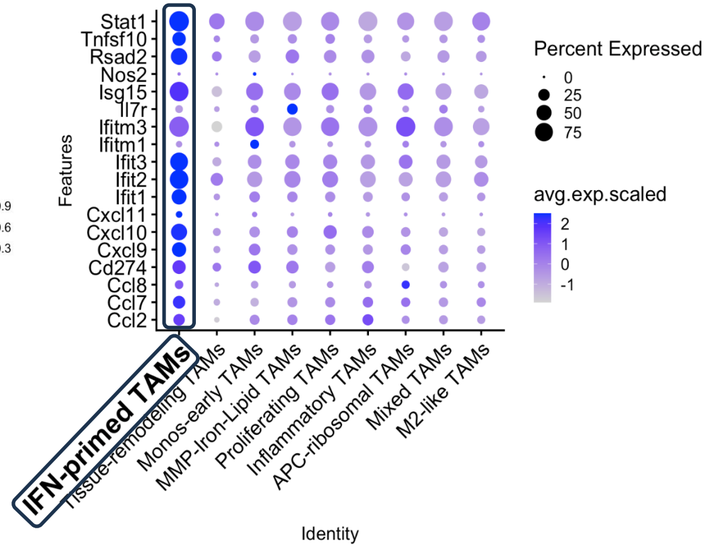


others ← → IFN-primed

IFN-primed TAMs marker expression (Ma, R.Y. 2022)

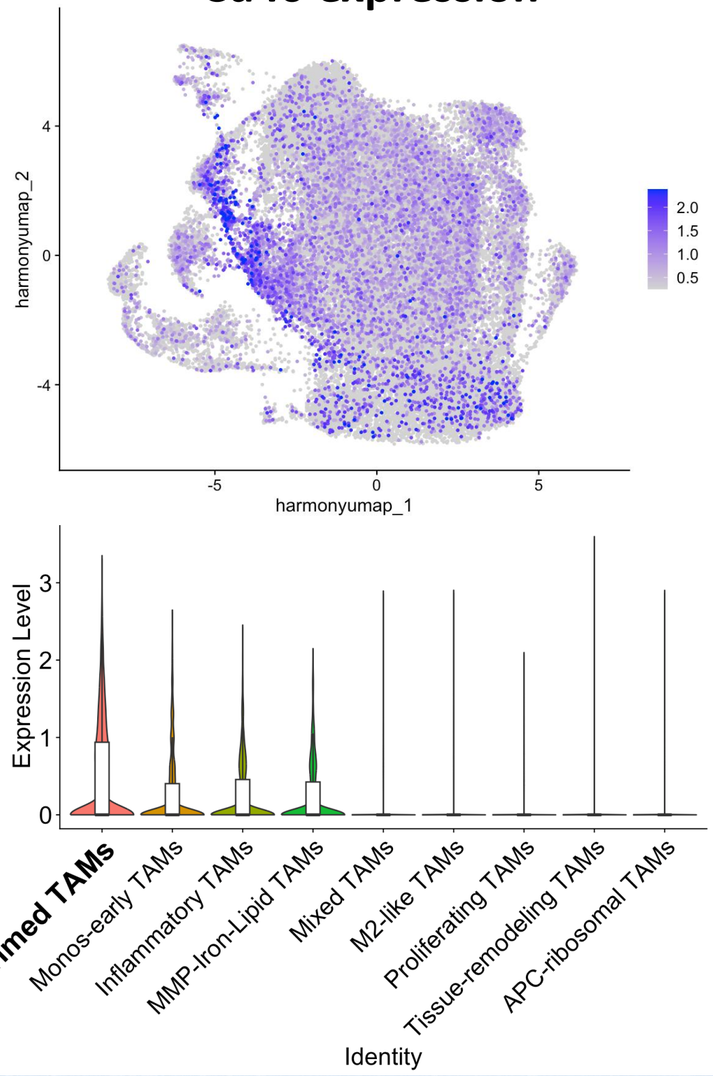




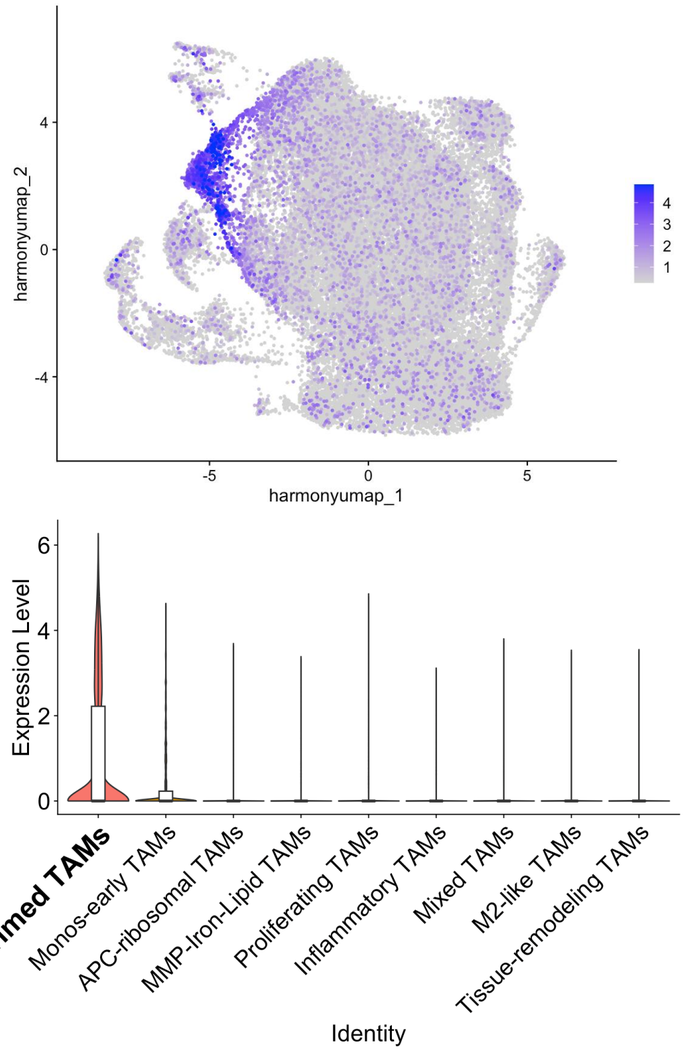
Ma, R.Y. *Trends in Imm* (2022)

Interferon-primed TAMs: select genes of interest

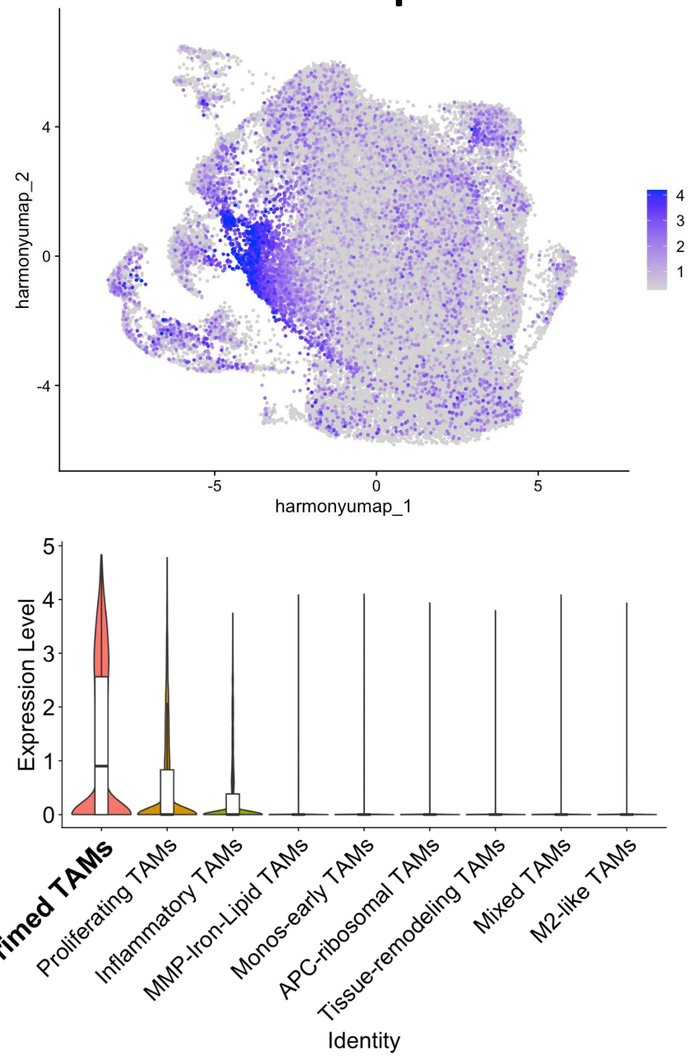
Cd40 expression



Cxcl9 expression



Cxcl10 expression



IFN-primed TAMs are immunotherapy-response TAMs

- CXCL9/10+ TAMs identified in multiple other cancer types
  - **Required for immunotherapy efficacy**

- Baseline TAM CXCL9/10 expression **predictive of immunotherapy response in humans**

- CXCL9/10 → **better OS** in humans

House, I.G. *Clin Can Res* (2020)
Qu, Y. *Cell Rep* (2020)
Garrido-Martin, E.M. *J Immunother Can* (2020)
Wei, C. *Precis Onc* (2024)

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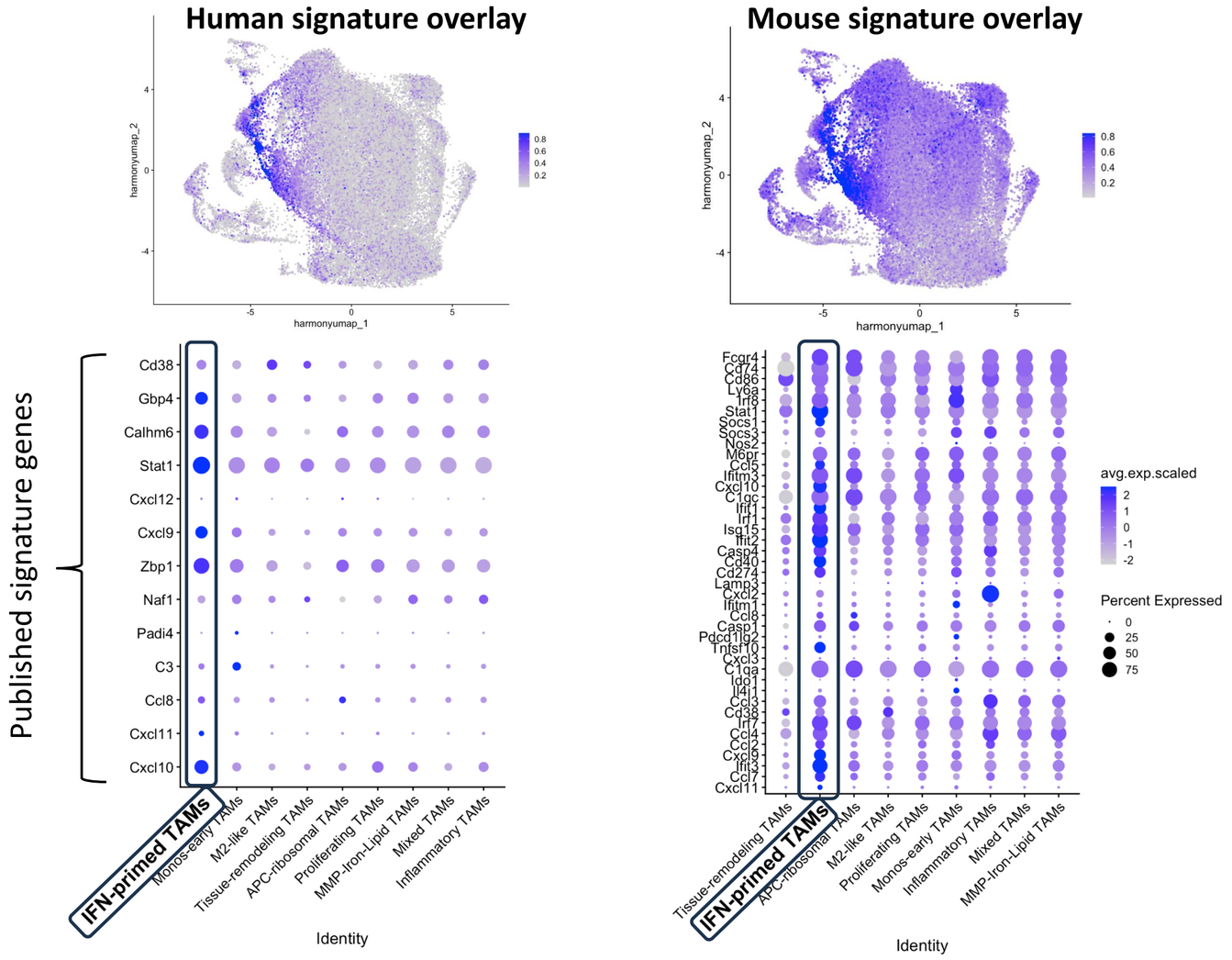
Immunotherapy-response signatures in mouse GIST TAMs



House, I.G. *Clin Can Res* (2020)
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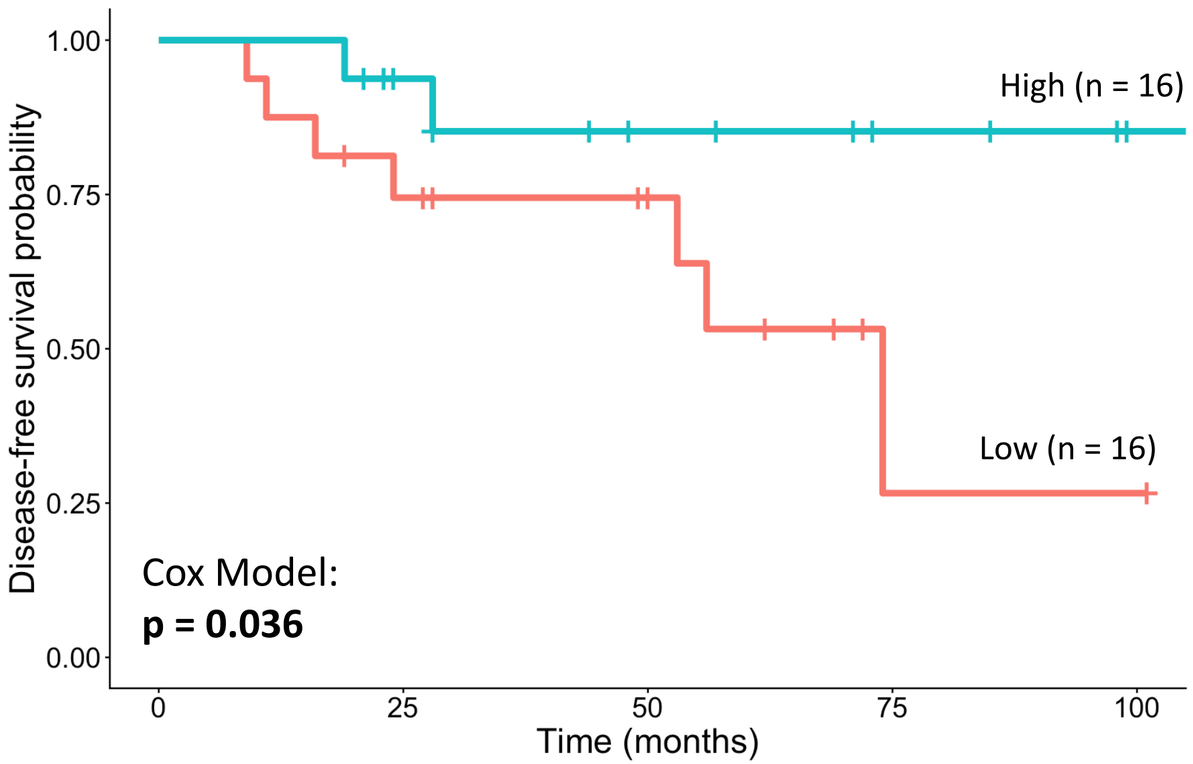
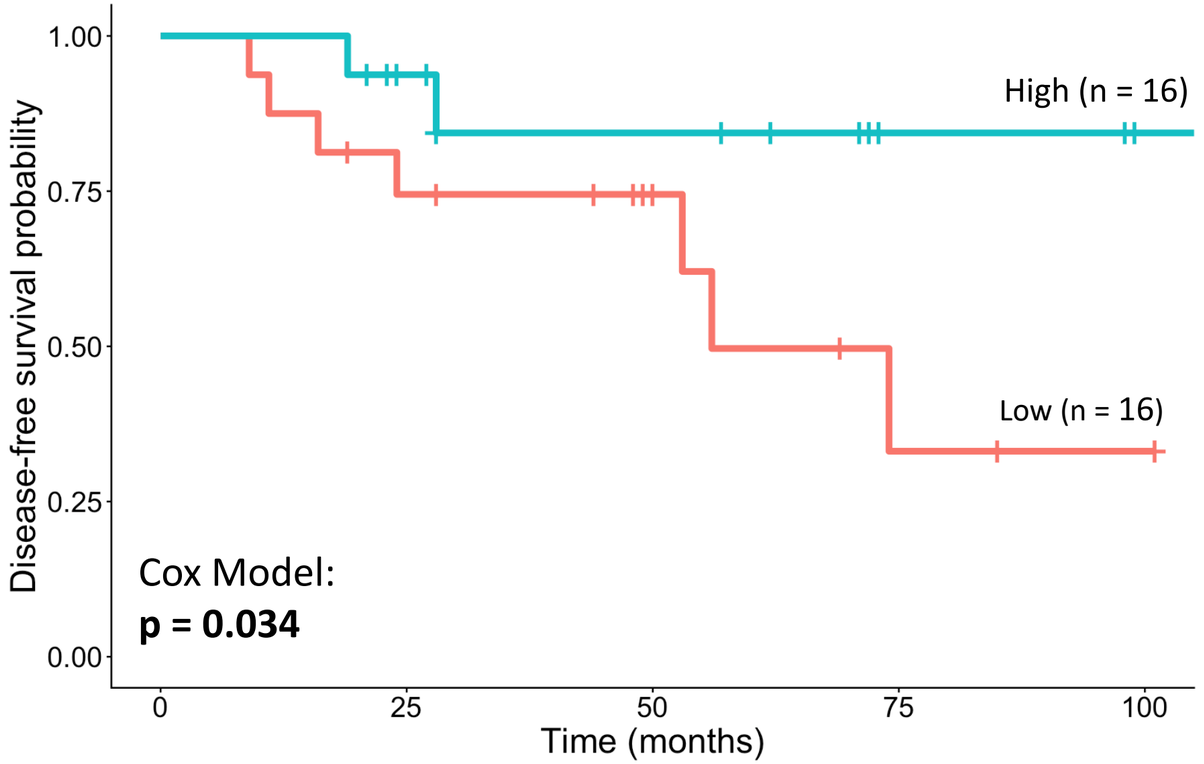
High CXCL9/10 in human GIST is prognostic of better overall survival

CXCL9 expression KM curve – median split

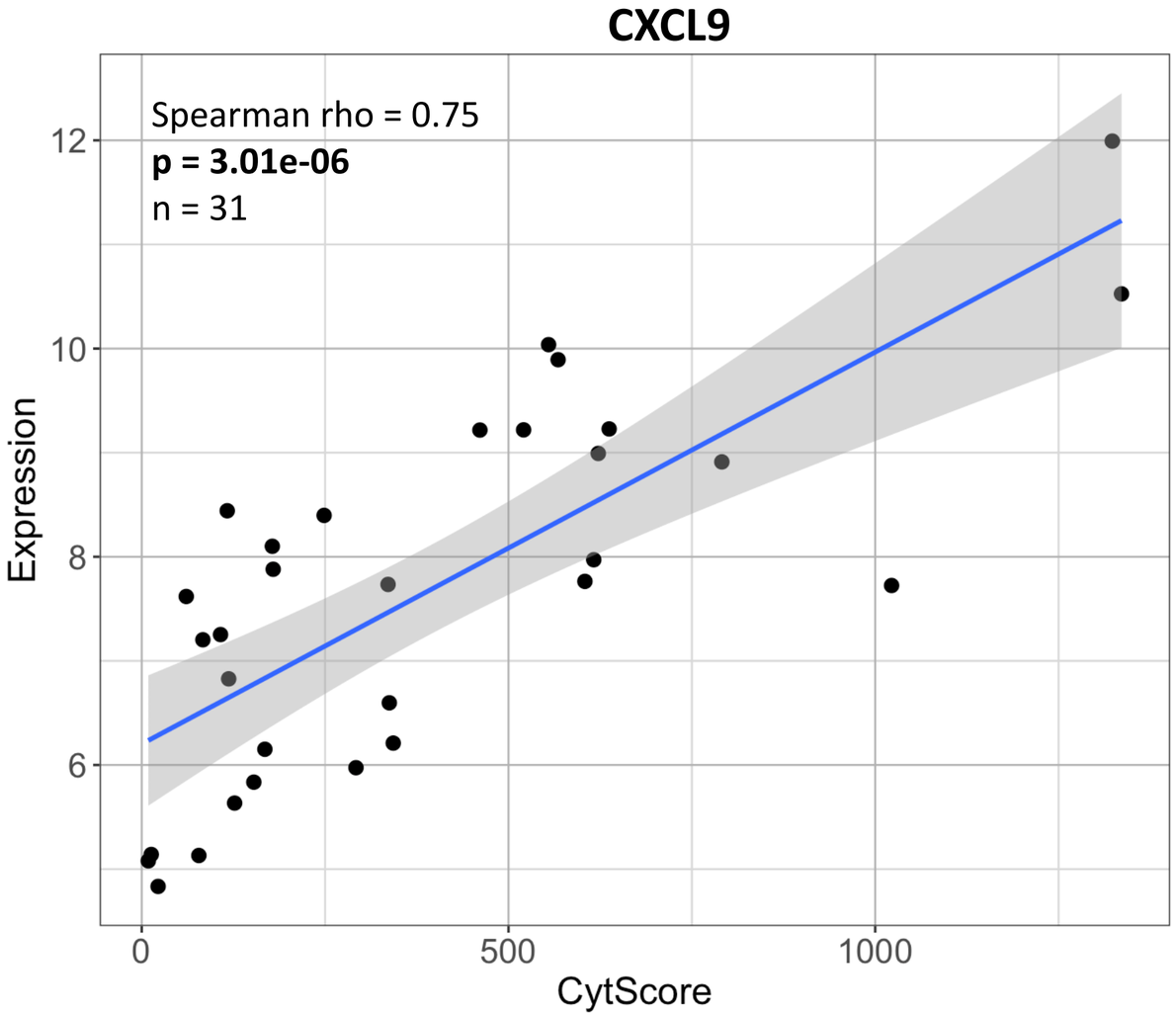


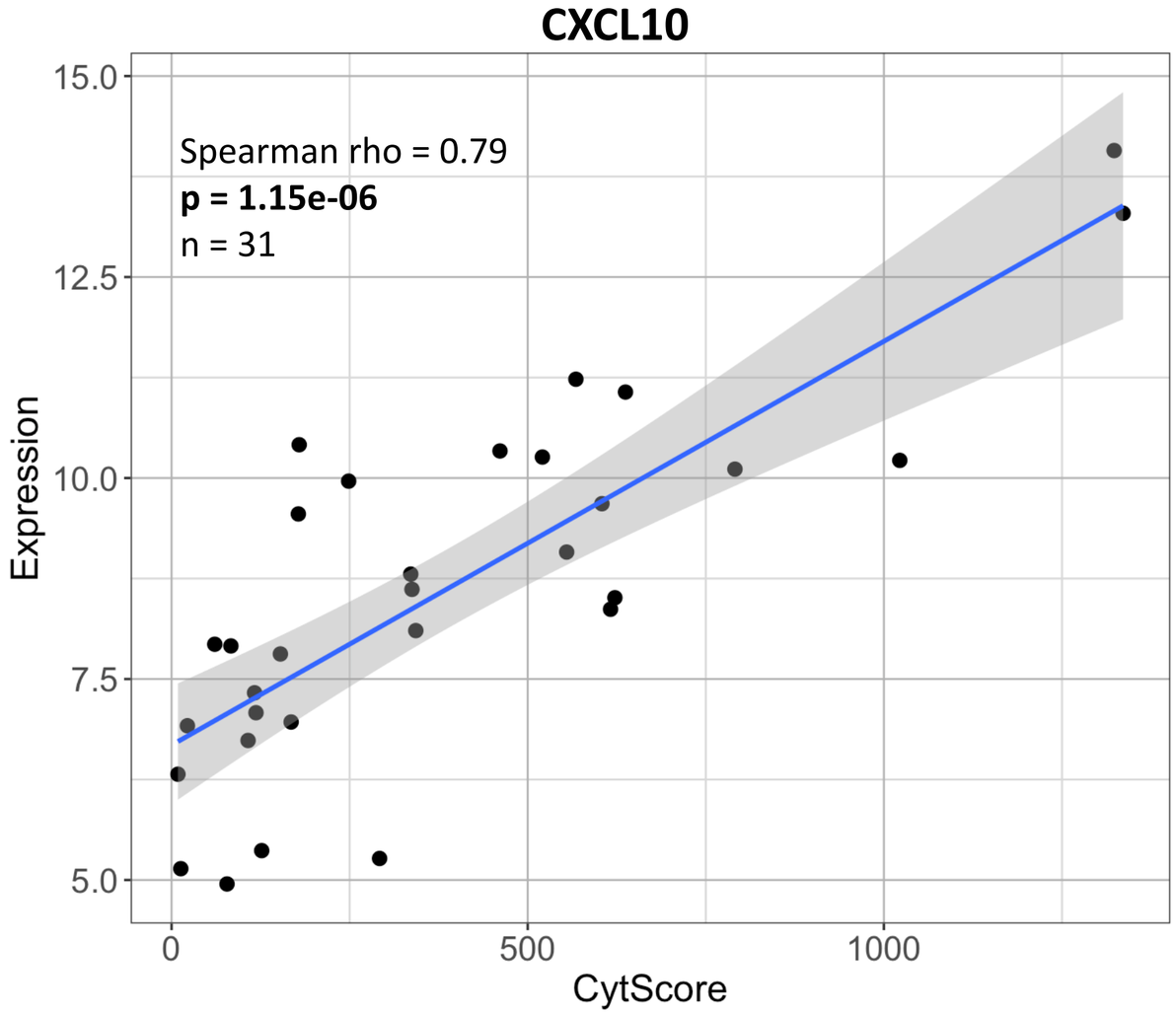
CXCL10 expression KM curve – median split



Yamaguchi, U. *J Clin Onc* (2008)

CXCL9/10 in human GIST correlates with cytotoxic immunity (CytScore)

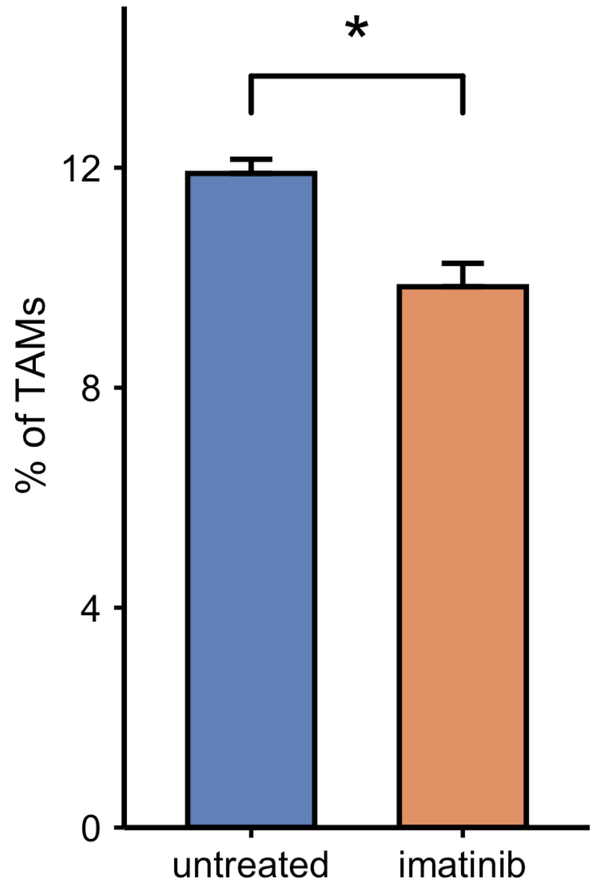




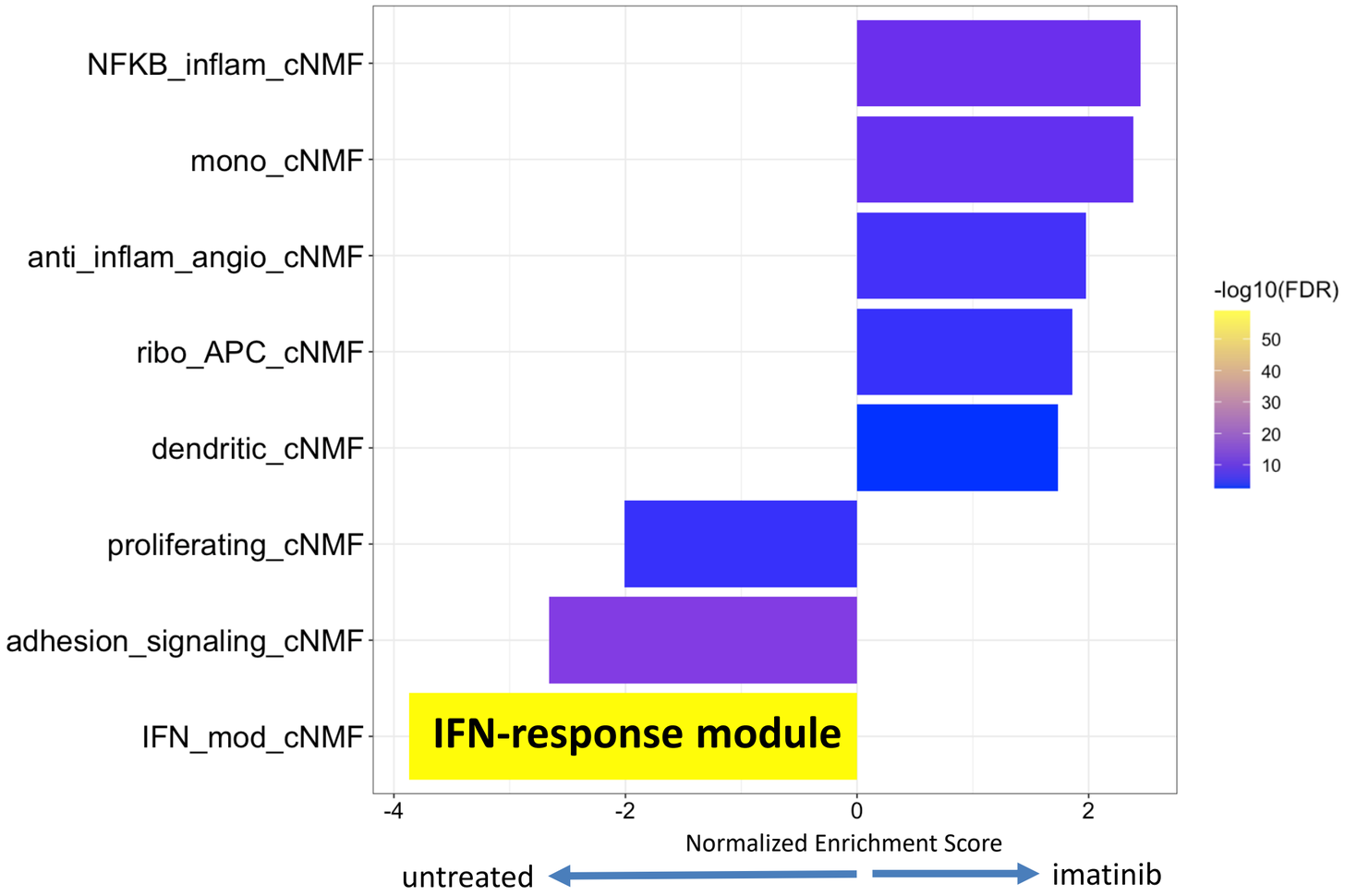
Rooney, M.S. *Cell* (2015)
Vitiello, G.A. *J Clin Inv* (2019)

Imatinib effects on IFN-primed TAMs in murine GIST

Imatinib decreases proportion of IFN-primed TAMs



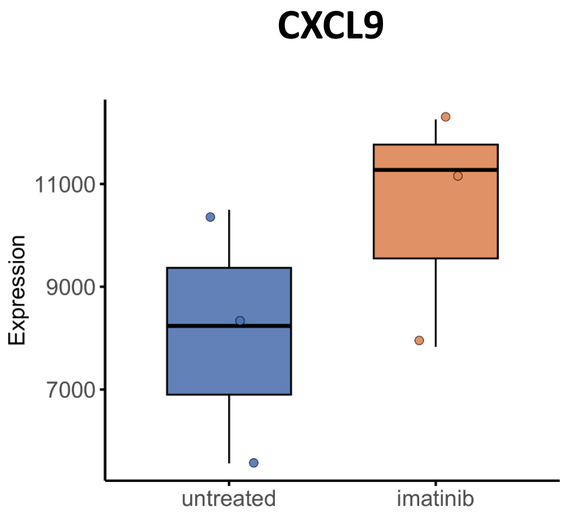
Imatinib decreases IFN-response module expression in GIST

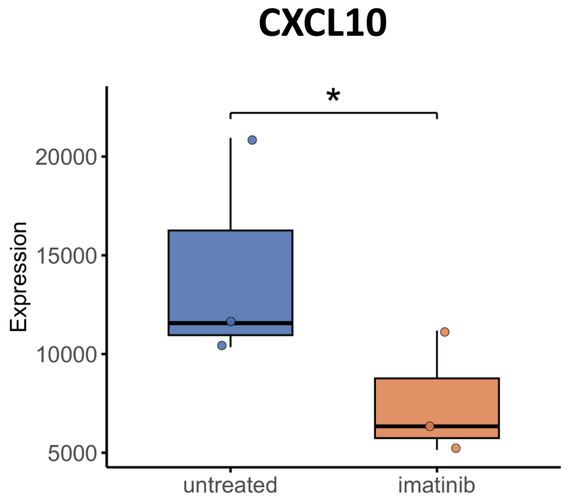


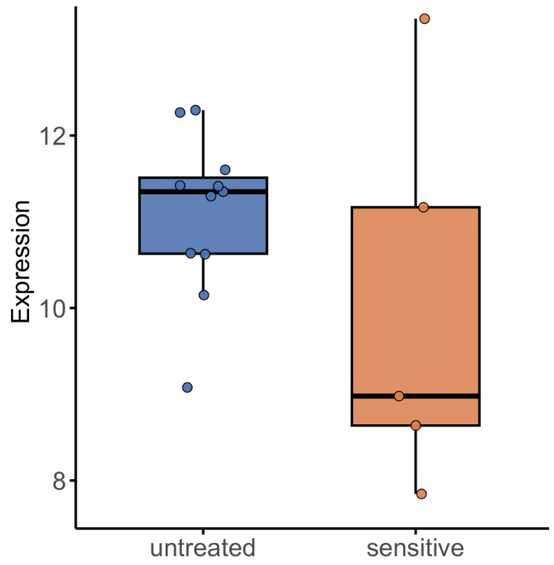
Imatinib effects on CXCL9/10 in GIST TAMs

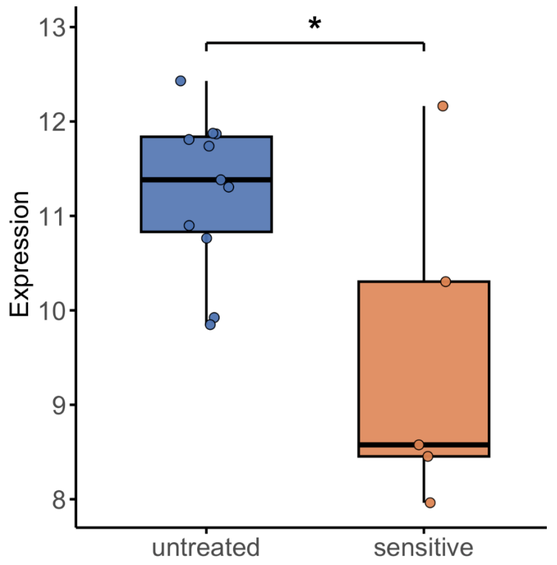
Mouse TAMs (1 week tx)

Human TAMs (~ 6 mo tx)
(Cavnar, M. 2013)







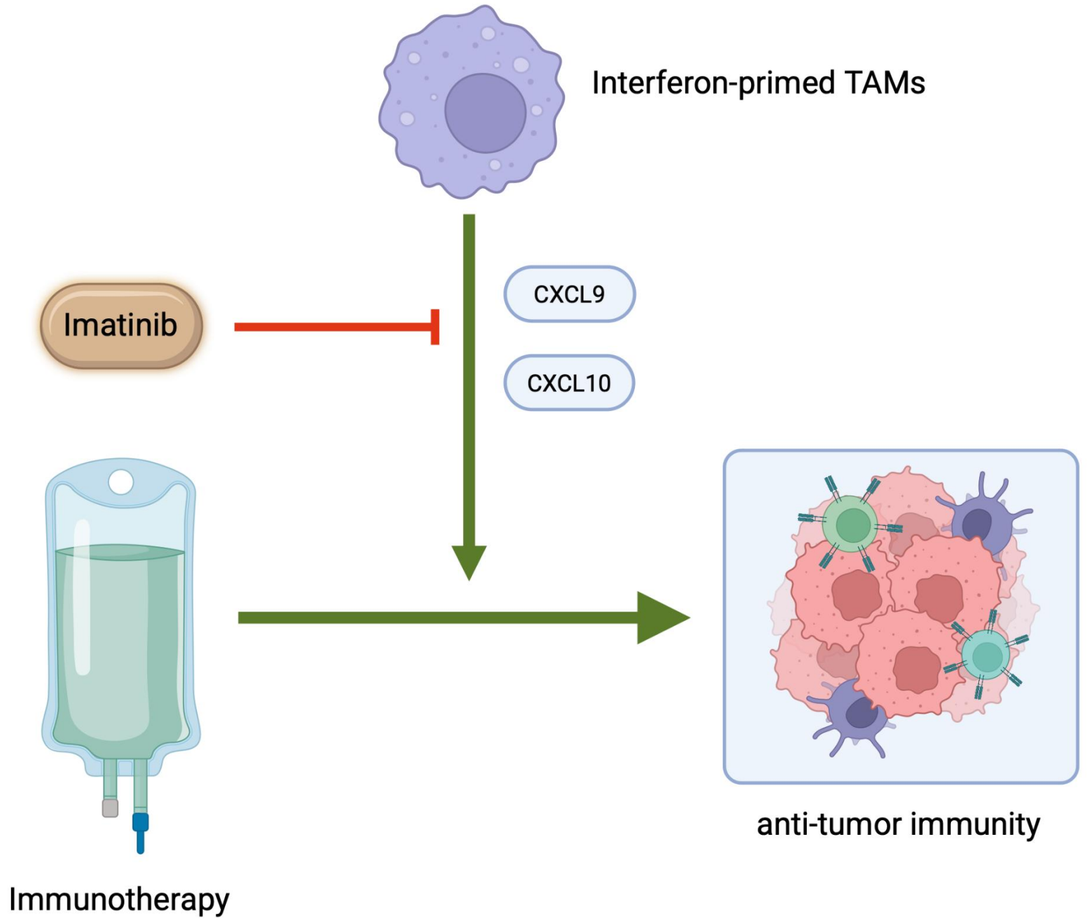


Cavnar, M. *J Exp Med* (2013)

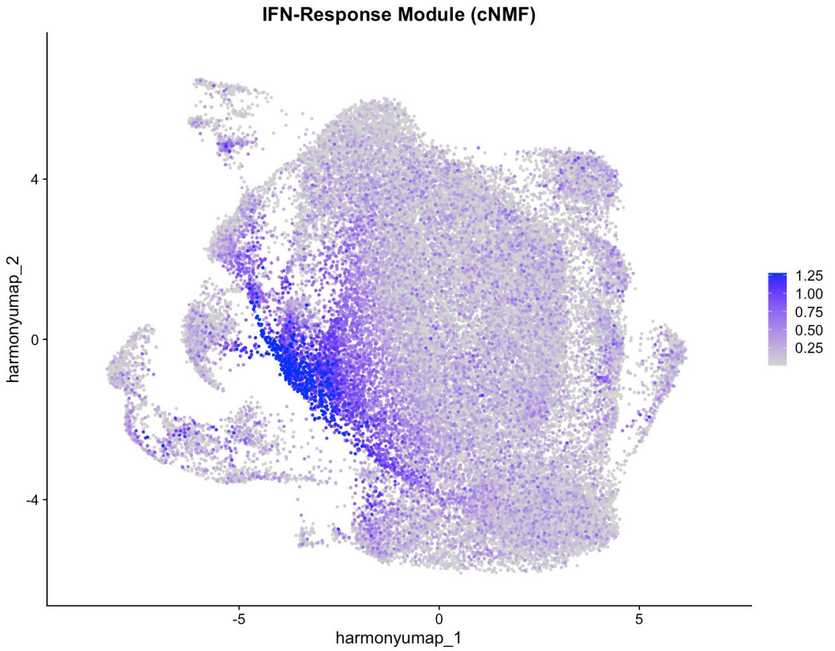
Imatinib as a barrier to immunotherapy in GIST

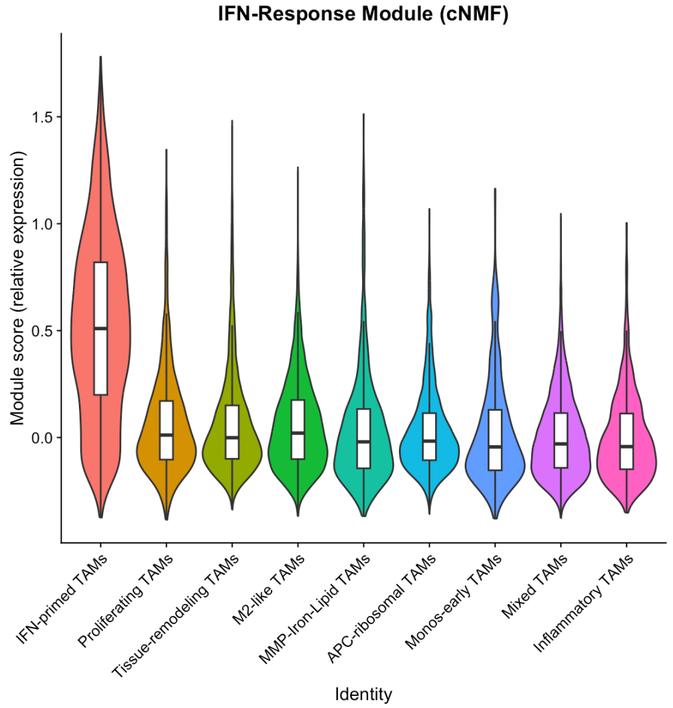
- Nearly all patients in GIST immunotherapy trials either on concurrent or previous TKI therapy

- **Pretreatment with immunotherapy?**

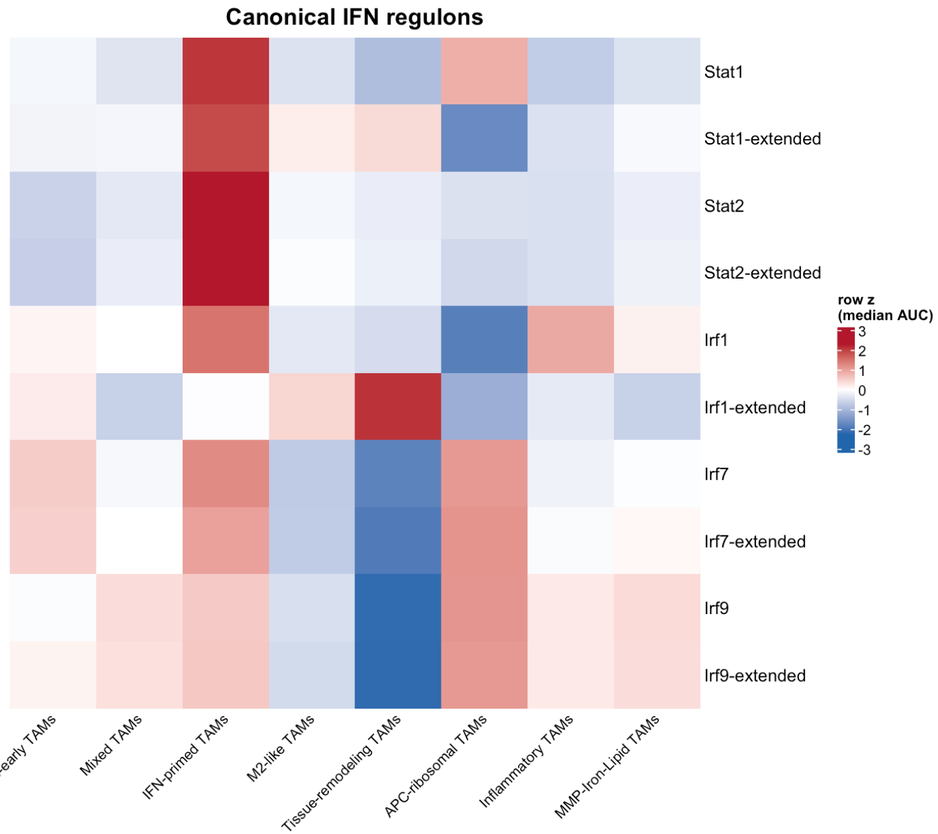


Interferon-primed TAMs: cNMF and SCENIC analysis





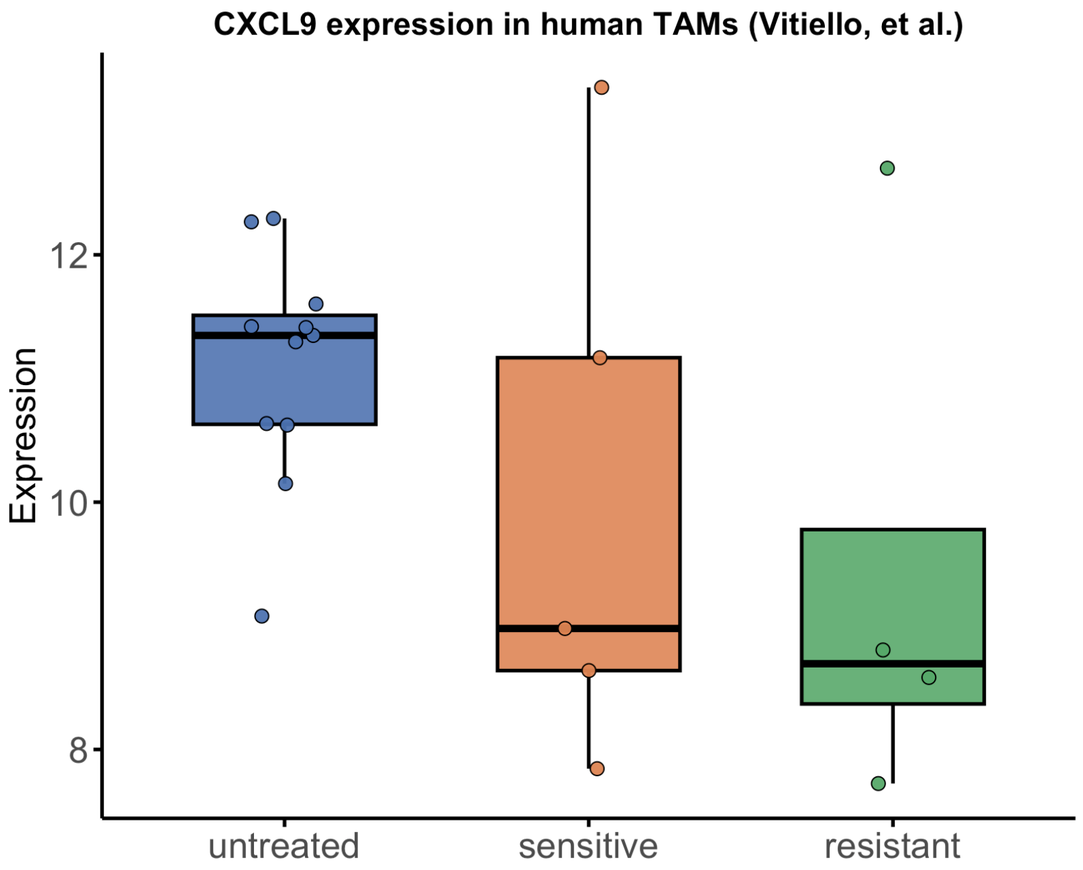
SCENIC analysis

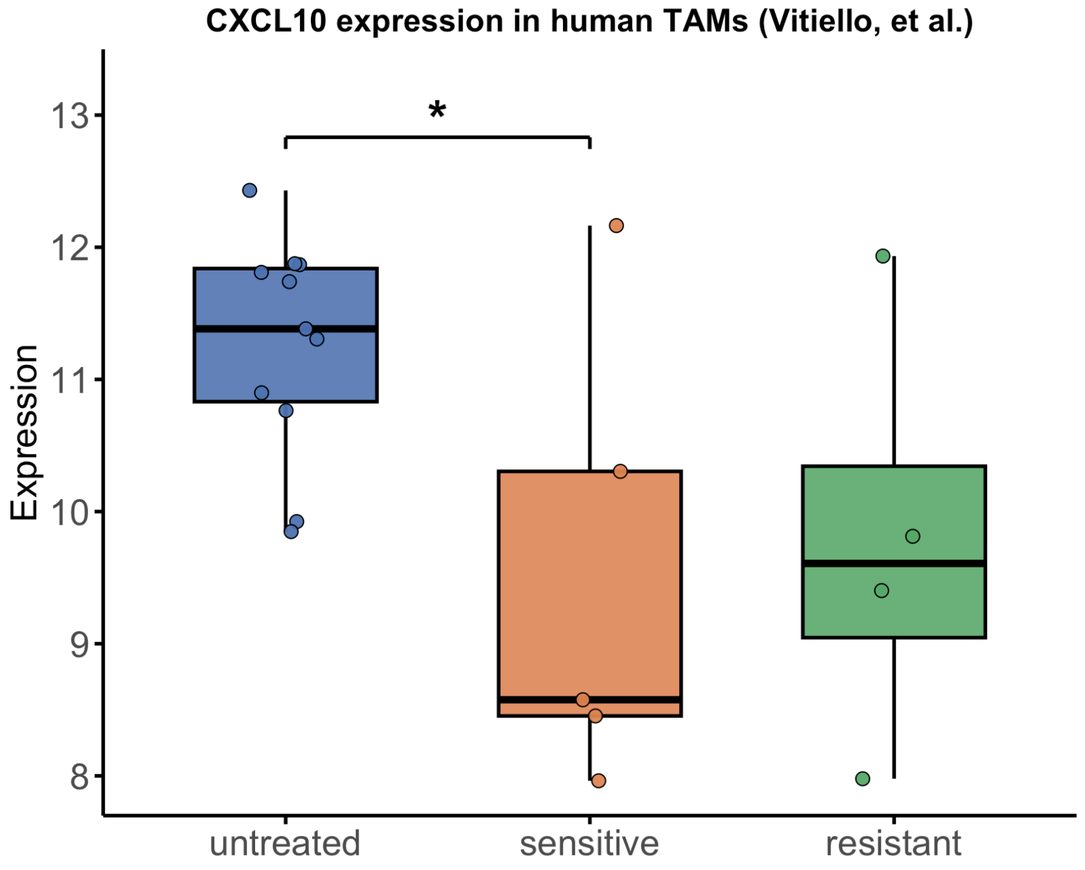


IFN-primed TAMs: drivers of antitumor immunity

Reference	Malignancy	Species/Model	Finding
House, et al., *Clin Can Res* (2020)	Triple negative breast	Mouse (orthotopic, syngeneic)	• **Bulk Cxcl9/10 expression increases with dual anti-PD-1, anti-CTLA-4 immune therapy** • **TAMs primary producers of CXCL9 on dual immunotherapy** • **TAMs required for efficacy of dual immunotherapy** • TAM depletion attenuated intratumoral CXCL9, CD8+ T cells • TAM Cxcl9 dependent on IFNg
	Colorectal	Mouse (heterotopic, syngeneic)	• **TAMs primary producers of Cxcl9/10 at baseline**
	Melanoma	Human	• Bulk CXCL9/10 expression higher in responders to dual immunotherapy , at baseline and on therapy • Bulk high CXCL9/10 associated with better OS on dual therapy, and CD8+ T cell infiltrate • **CXCL9/10 higher in TAMs from immunotherapy responders**
	Urothelial carcinoma	Human	• Bulk CXCL9/10 expression prognostic indicators • Bulk higher CXCL9/10 expression in anti-PD-L1 responders, correlated with T cell infiltrate
	Triple negative breast	Human	• Bulk high CXCL9/10 associated with improved OS, with standard of care
	NSCLC, head and neck, melanoma	Human	• **TAMs primary producers of CXCL9/10**
Wen, et al., *Cell Rep* (2020)	Colorectal	Mouse (heterotopic, syngeneic)	• **Final Cxcl9/10 expressing TAM abundance positively correlated with anti-PD-L1 response,** also enriched for IFN response • **CXCL9 required for anti-PD-L1 response, but depletion had no effect alone**
	Multiple solid tumors	Human	• High bulk CXCL9/10 expression associated with improved OS
Garrido-Martin et al., *J Immunother Can* (2020)	NSCLC	Human	• "M1-hot" TAMs have high CXCL9/10 expression, abundance correlated with CD8+ T cell infiltrate • Tumors with high density of CXCL9 high cells associated with better OS
Wei, et al., *Precis Onc* (2024)	Melanoma	Human	• Anti-tumoral TAMs enriched for CXCL9/10 and interferon response • **CXCL9/10 higher in TAMs from immunotherapy responders**

Imatinib effects on CXCL9/10 in GIST TAMs





Cavnar, et al., *J Exp Med* (2013)