Immunity in GIST

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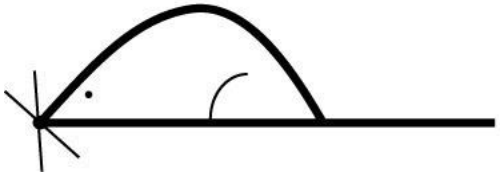
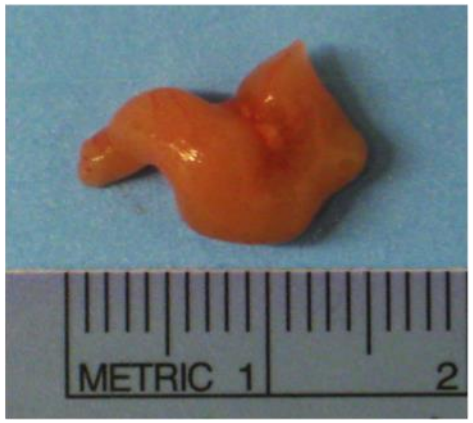
How do we cure GIST?

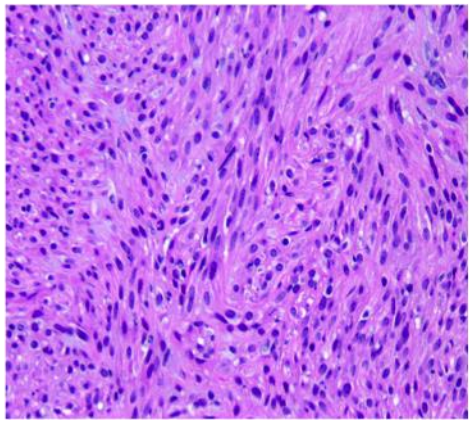
- Adjuvant therapy
- Surgery for residual metastatic disease
- Other tyrosine kinase inhibitors
- Immune therapy

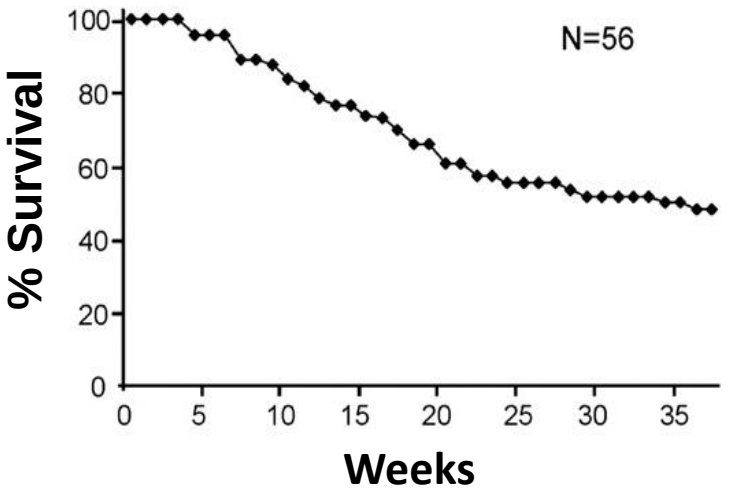
Murine model of GIST

Deletion mutation in *KIT* exon 11



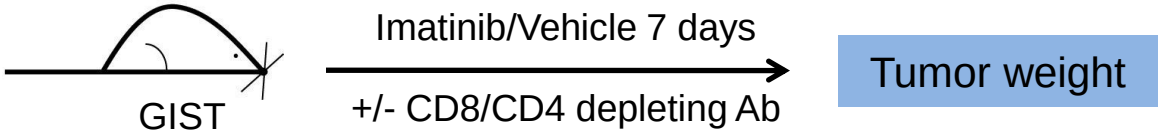


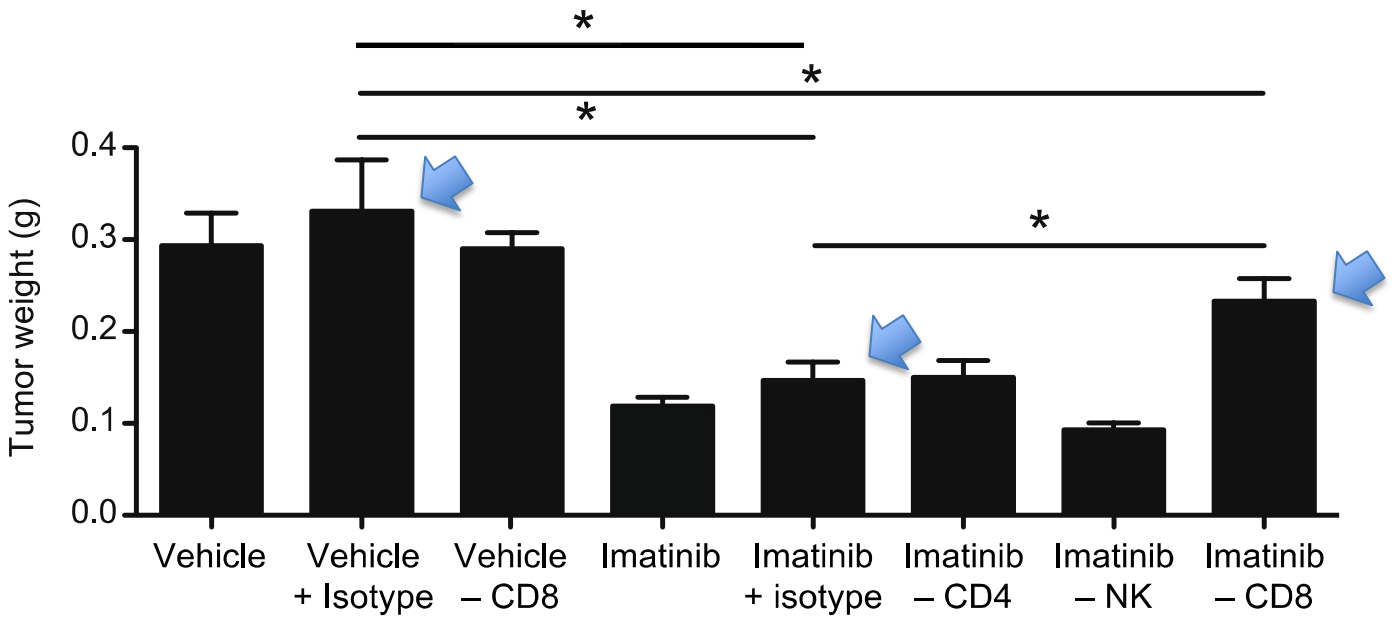




Sommer, PNAS 2003; 100:6706

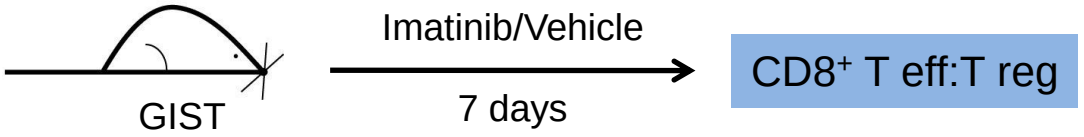
CD8+ T cells contribute to imatinib's effects

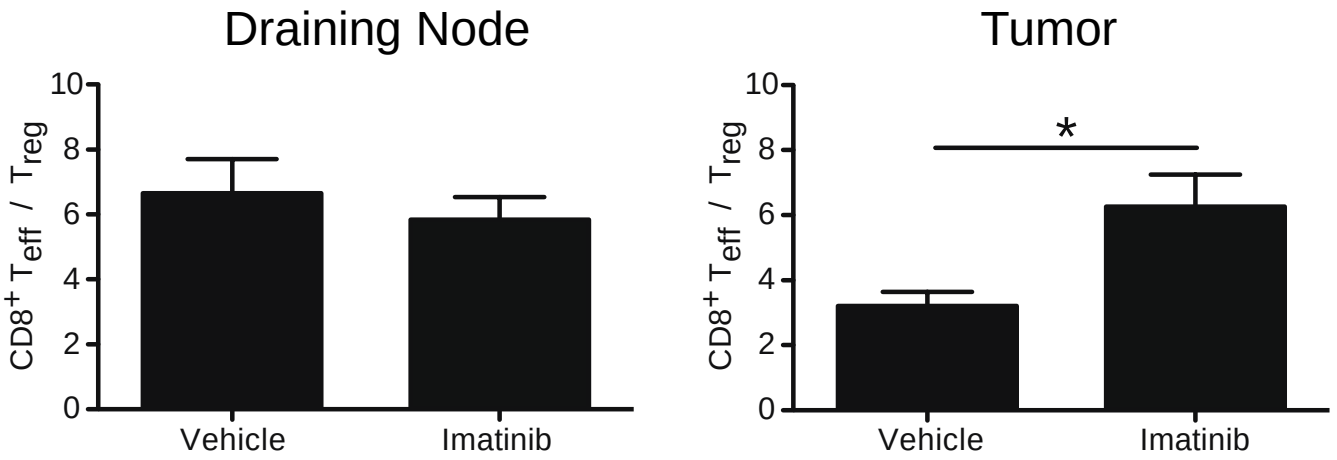




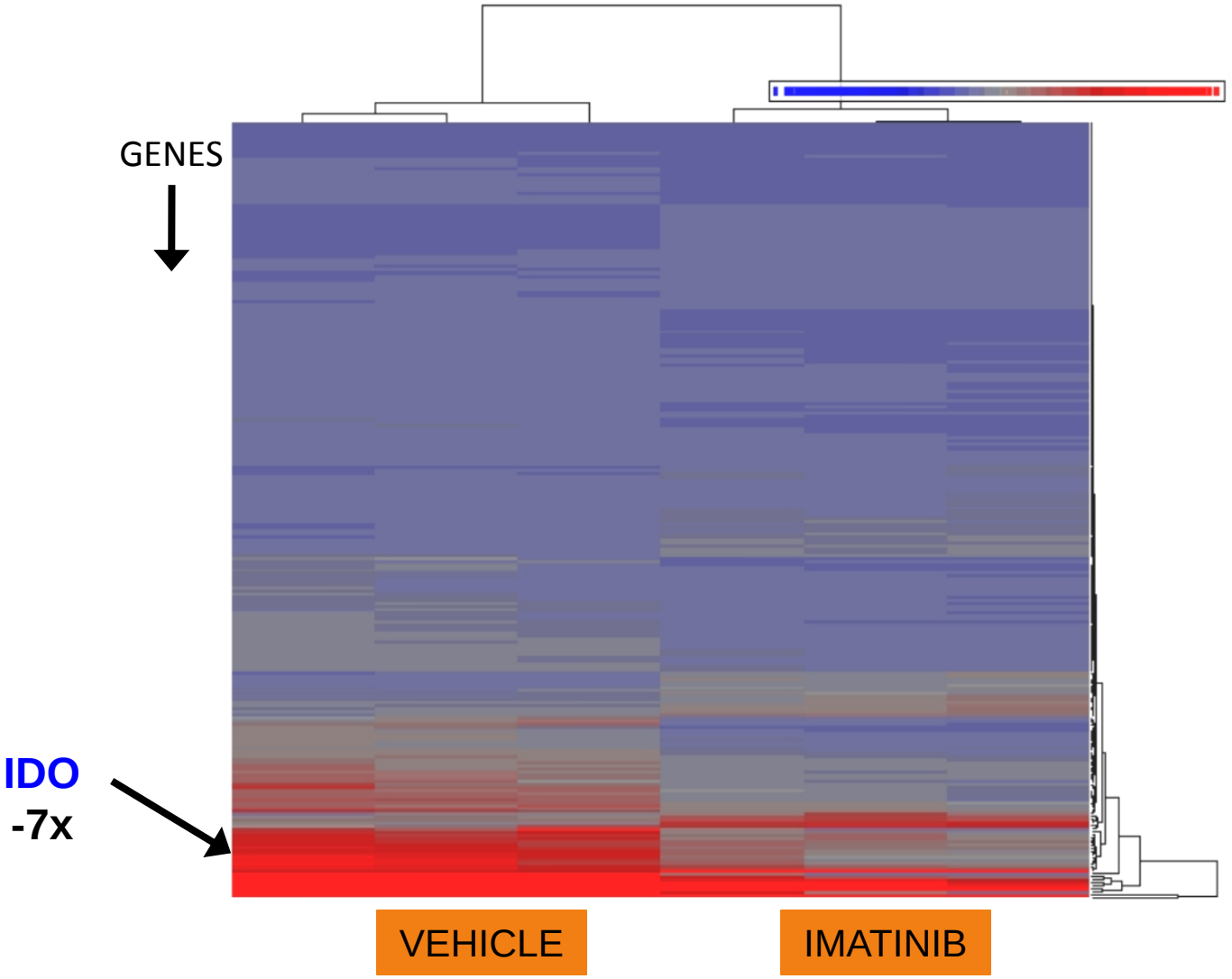
Nature Med 2011; 17:1094

Imatinib increases intratumoral T eff:T reg ratio



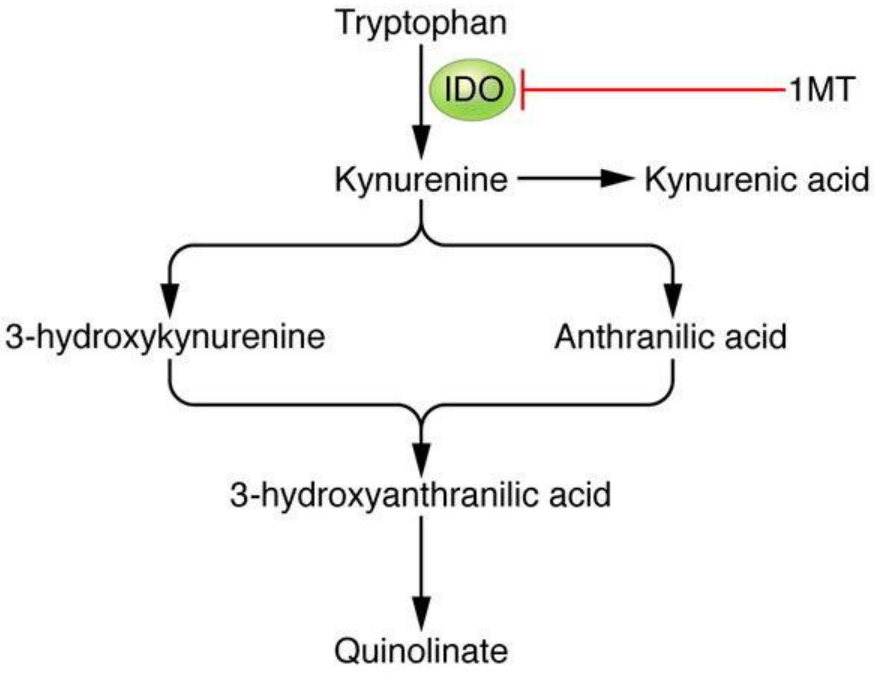


How does imatinib modulate T eff:T reg?



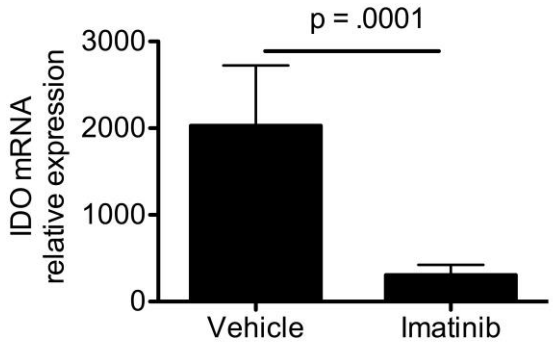
Indoleamine 2,3-dioxygenase (IDO)

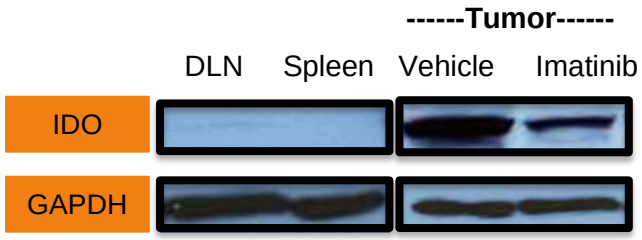
- Catalyzes tryptophan to immunosuppressive metabolites
- Inhibits maternal T cell immunity during gestation
- Induces T cell tolerance in tumor, infection, autoimmunity

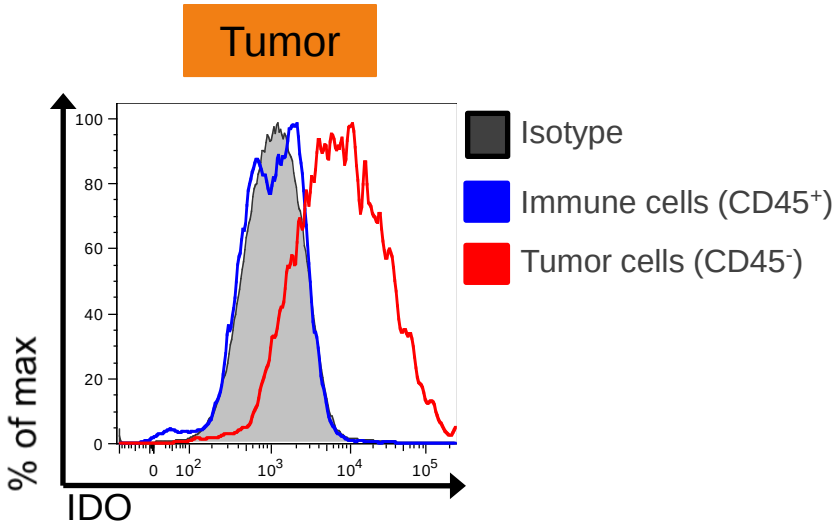


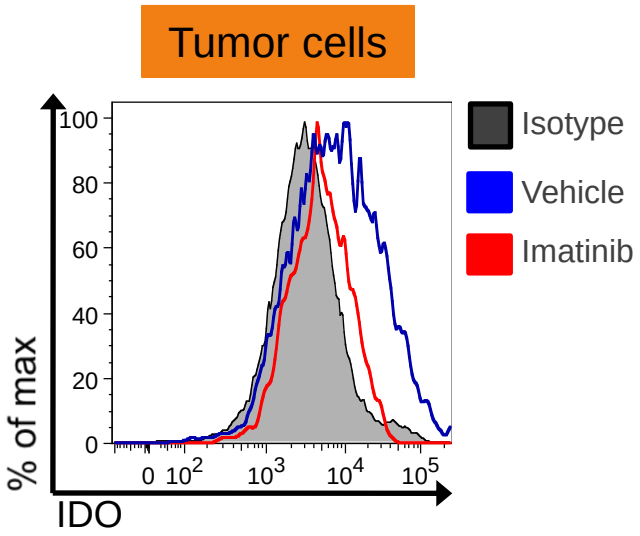
Munn, JCI 2007; 117:1147

Imatinib inhibits tumor cell IDO

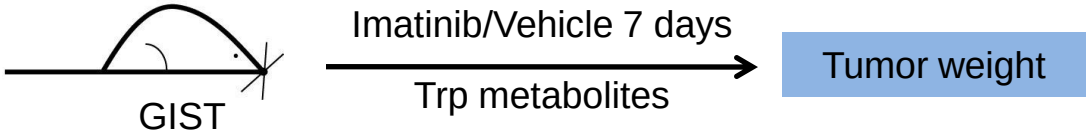


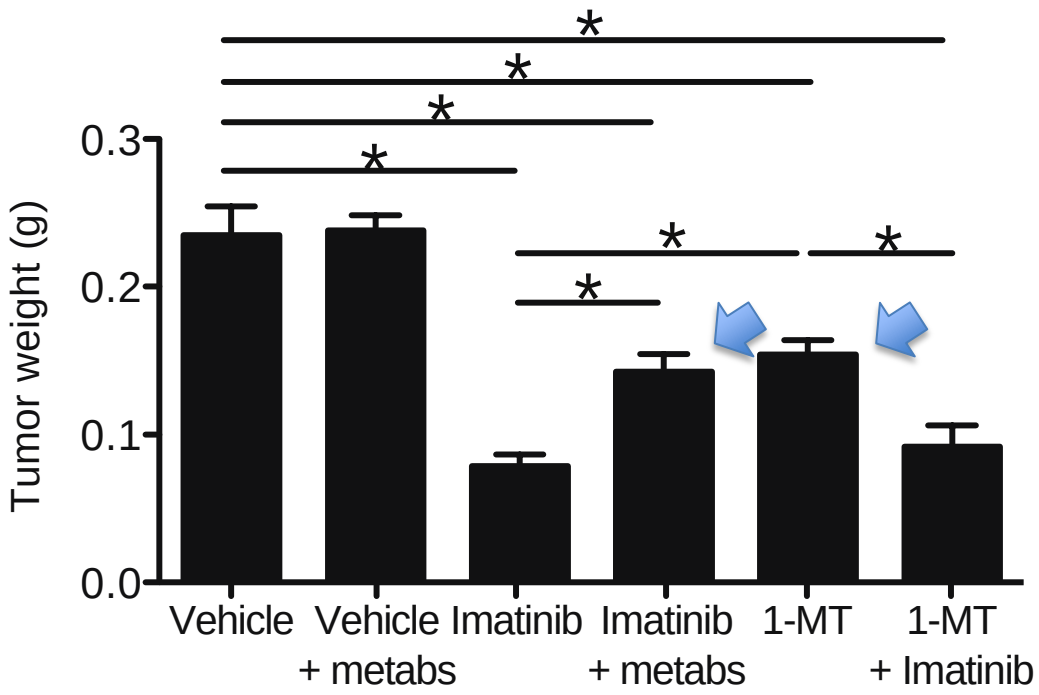




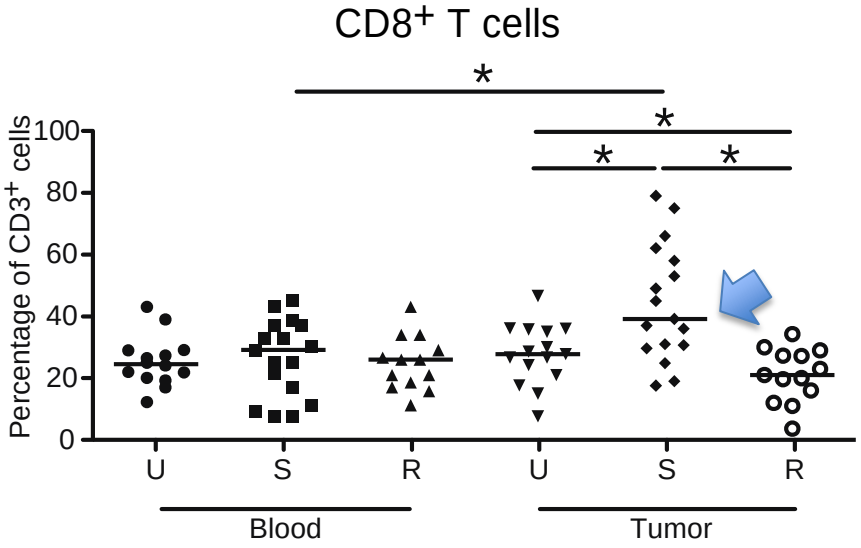


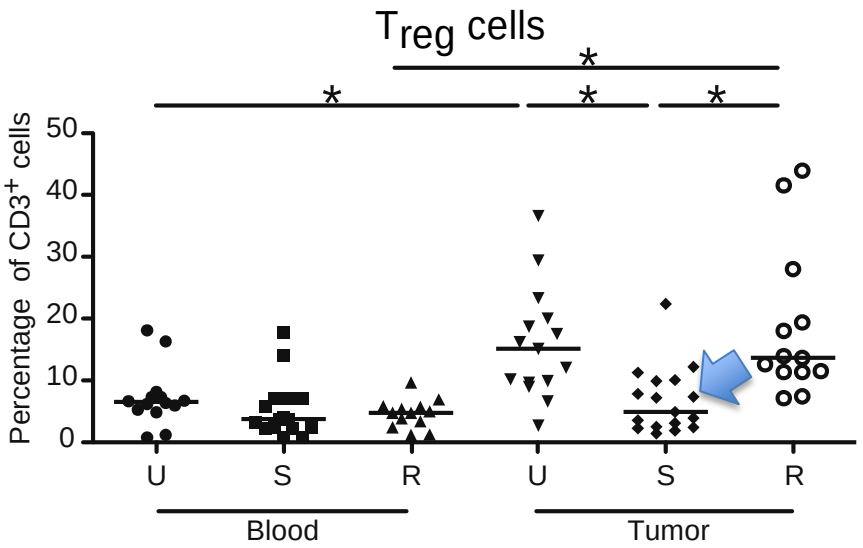
IDO inhibition contributes to imatinib's effects

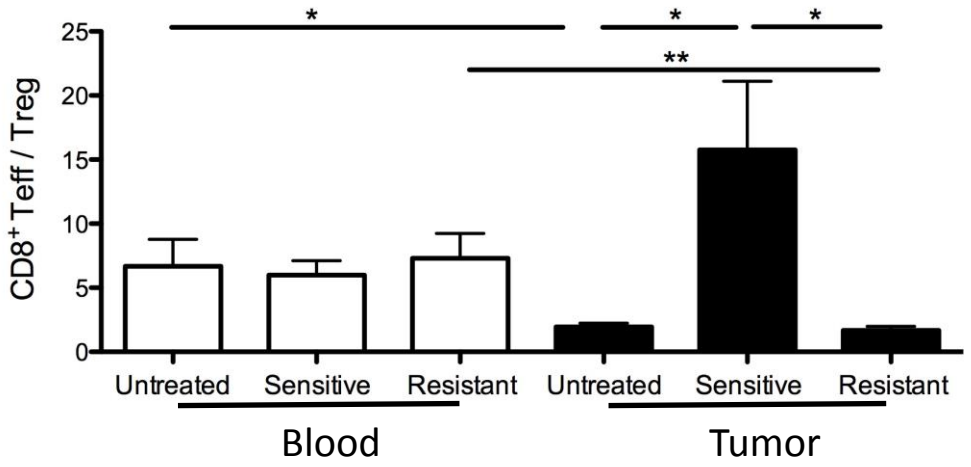




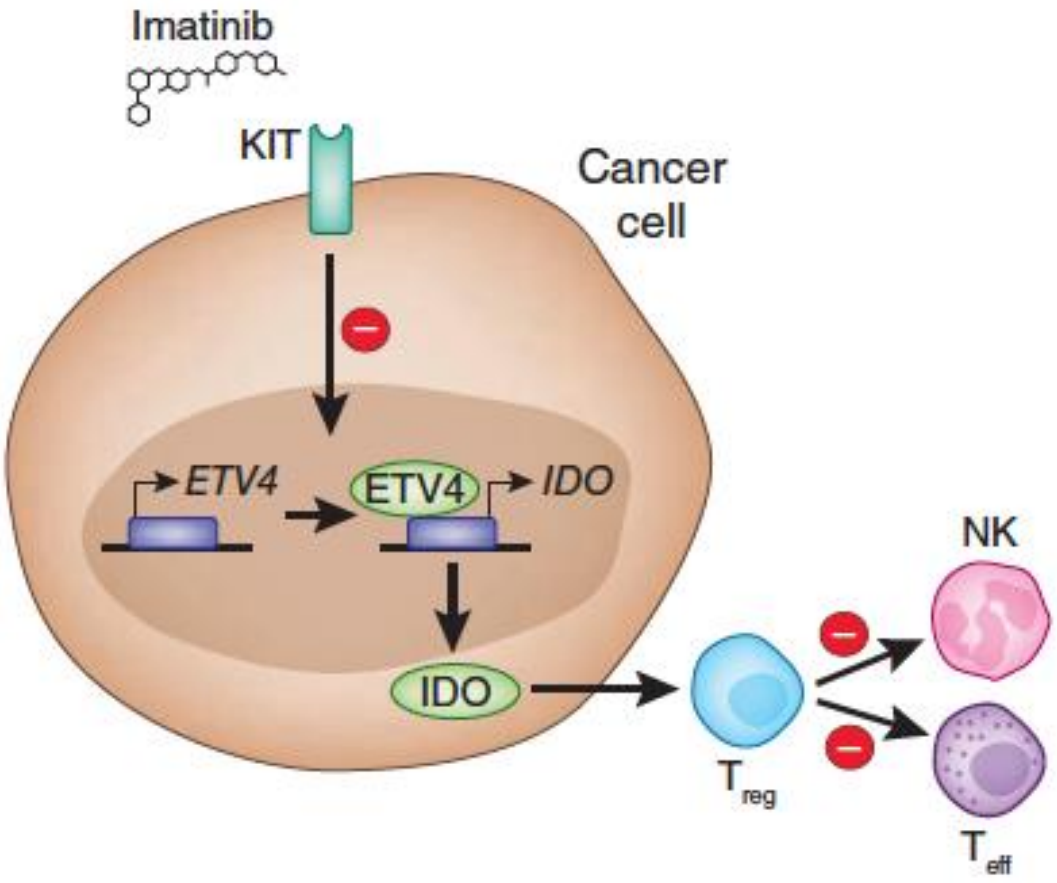
CD8:T reg correlates with imatinib sensitivity in human GIST (N=45 specimens)





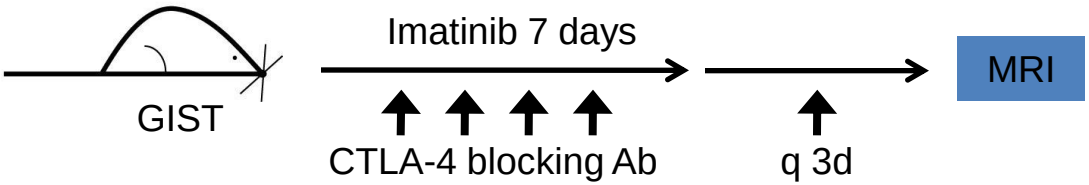


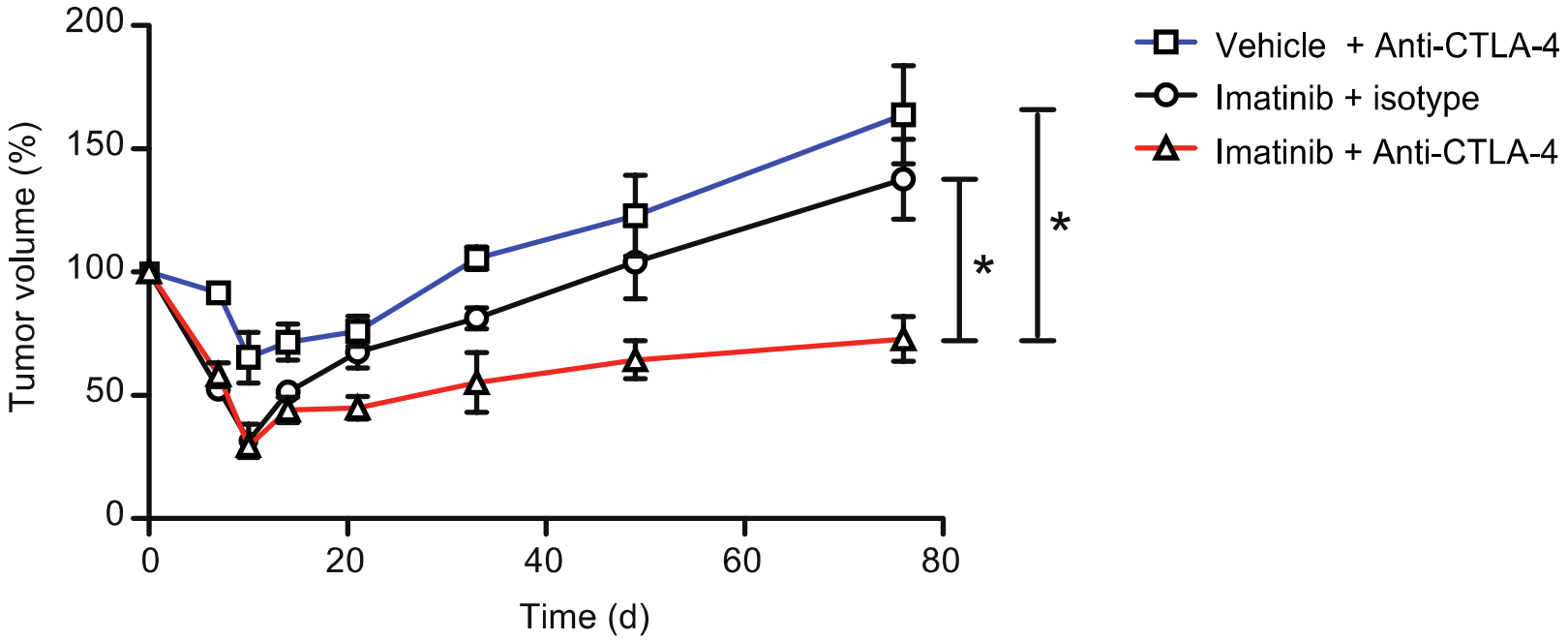
Mouse and Human T Cells in GIST



Zitvogel and Kroemer, Nat Med 2011; 17:1050

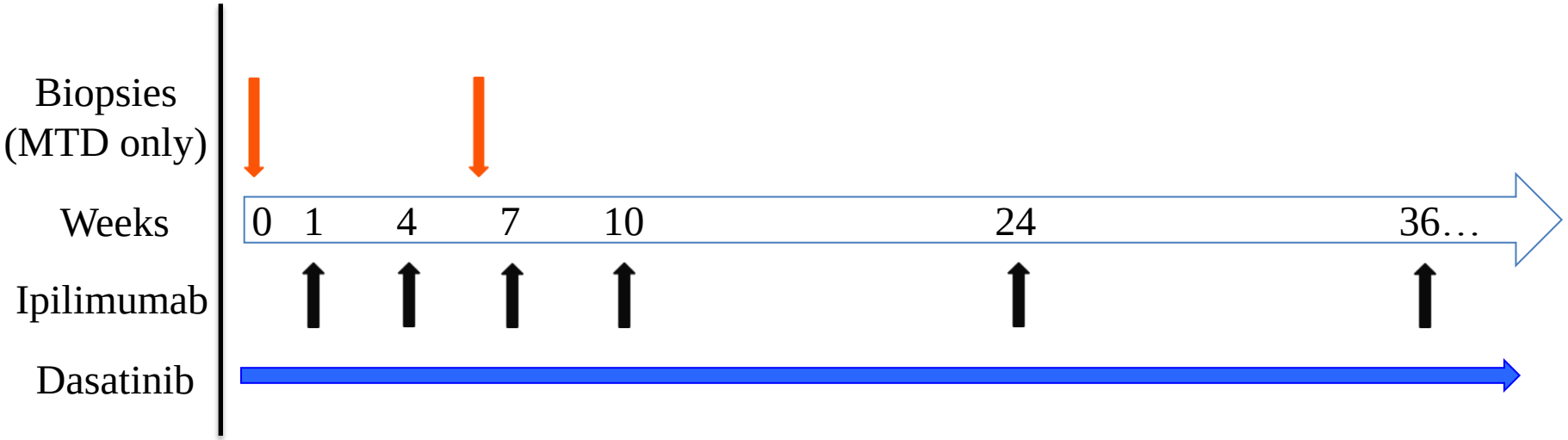
Imatinib synergizes with anti-CTLA-4 in mouse GIST





Phase I Trial of 3rd Line Dasatinib + Ipilimumab

Dose Level	Dasatinib	Ipilimumab
1	70 mg QD	10 mg/kg
2	100 mg QD	10 mg/kg
3	140 mg QD	10 mg/kg



3x3 design with an expansion phase of 12

Sponsored by NCI and Bristol-Meyers
ASCO 2014 Abstract 10251

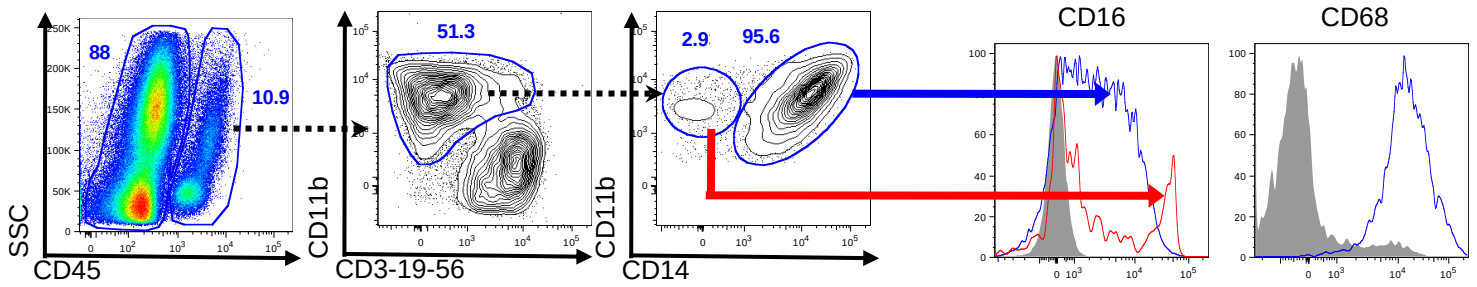
Tumor-associated Macrophages (TAMs)

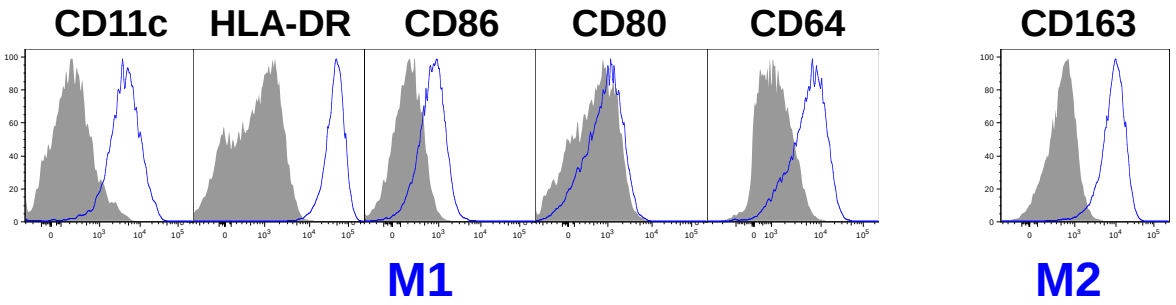
	M1	M2
Induced by	IFN-γ	IL-4
Class II, CD11c	High	Low
Secrete	TNF, IL-12	IL-10
Effect on T cells	+	-
Effect on tumors	**-**	**+**

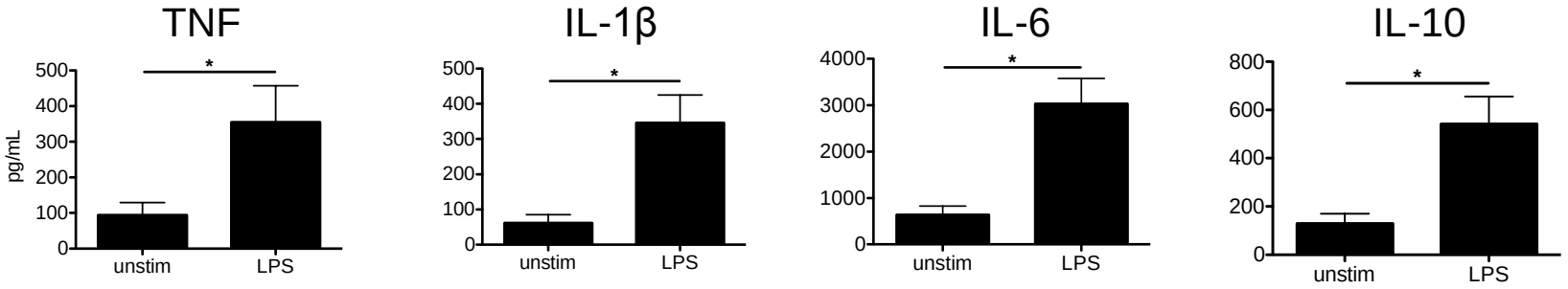
TAMs are M2 in mouse subcutaneous tumors and in human tumors

Biswas & Mantovani, Nat Immunol 2010
Movahedi K, Cancer Res 2010

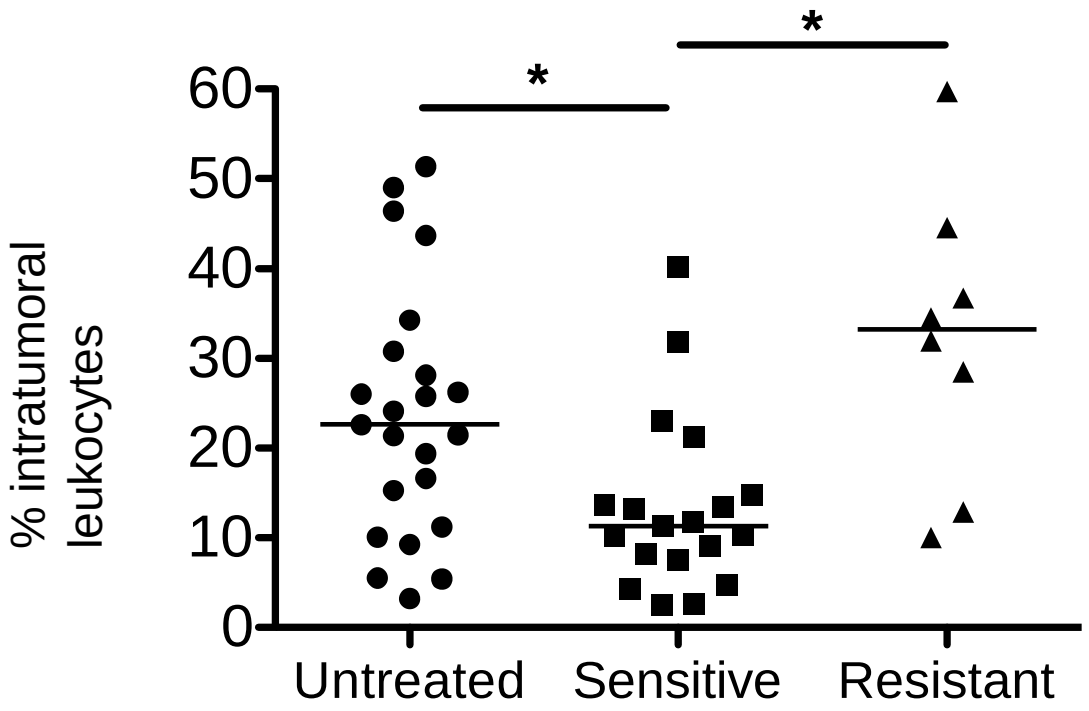
TAMs infiltrate *human* GIST







TAMs are reduced by imatinib in human GIST (N=57)



Human GIST TAMs become M2 with imatinib

10 sensitive, 5 sensitive, 4 resistant

M1 ↓

HLA-DQA1	major histocompatibility complex, class II, DQ alpha 1	**-34.3**
HLA-DQB1	major histocompatibility complex, class II, DQ beta 1	**-23.9**

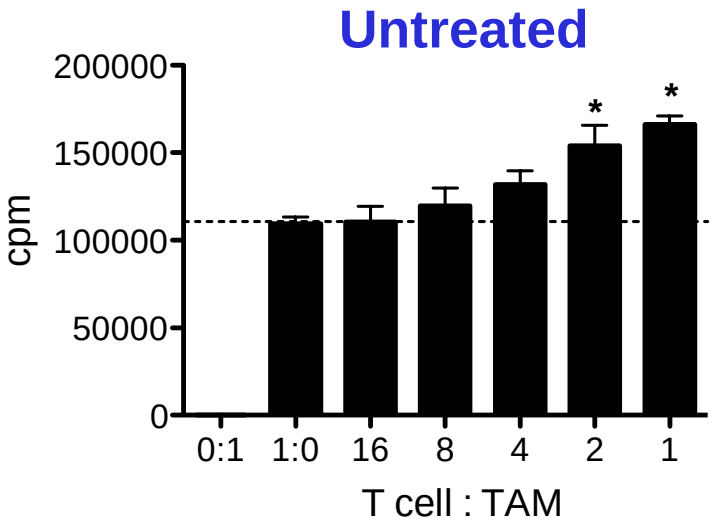
M2 ↑

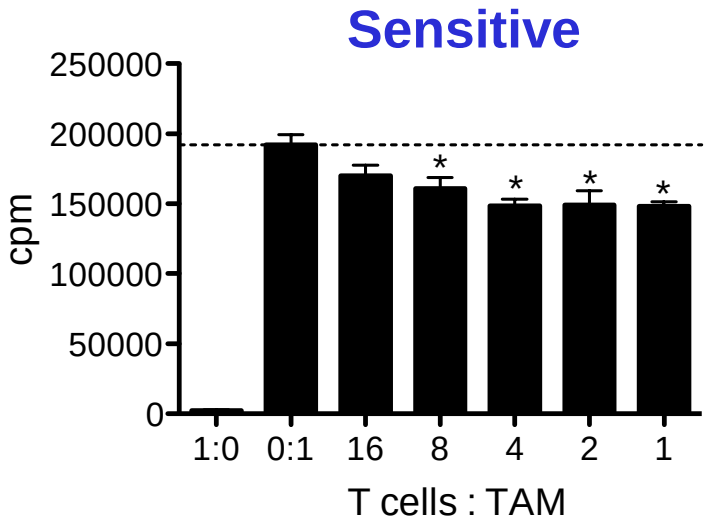
CHI3L1 *	chitinase 3-like 1 (cartilage glycoprotein-39)	**+22.1**
CHIT1	chitinase 1 (chitotriosidase)	**+4.7**
MARCO	macrophage receptor with collagenous structure	**+4.2**
PLA2G7 *	phospholipase A2, group VII (platelet-activating factor acetylhydrolase, plasma)	**+3.1**
IL1RN	interleukin 1 receptor antagonist	**+3.8**
ARG1	arginase, liver	**+7.5**
FOLR3	folate receptor 3 (gamma)	**+3.3**
MMP25	matrix metallopeptidase 25	**+2.4**
MMP19	matrix metallopeptidase 19	**+4.3**
MMP7	matrix metallopeptidase 7 (matrilysin, uterine)	**+4.6**
MME	membrane metallo-endopeptidase	**+7.6**
HAS2	hyaluronan synthase 2	**+2.6**
HAS1	hyaluronan synthase 1	**+2.9**
HS3ST2	heparan sulfate (glucosamine) 3-O-sulfotransferase 2	**+5.5**
COL6A2	collagen, type VI, alpha 2	**+2.6**
ANGPTL4	angiopoietin-like 4	**+2.2**
ANGPT2	angiopoietin 2	**+2.5**
CTSK	cathepsin K	**+2.9**
CTSD	cathepsin D	**+3.0**

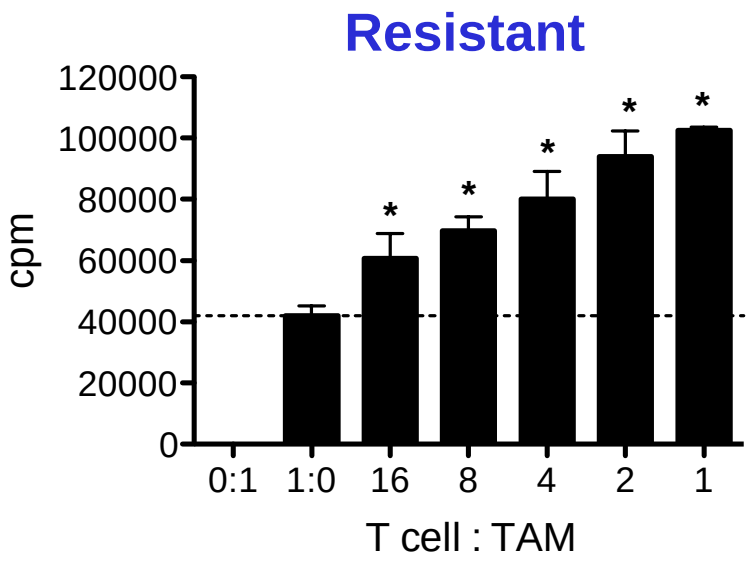
Untreated vs. Sensitive
689 genes

Untreated vs. Resistant
0 genes

Human TAMs become M2 with imatinib therapy







Intratumoral macrophages in GIST

Baseline	**Imatinib sensitive**	**Imatinib resistant**
High %	Low %	High %
M1	M2	M1
T cell stimulation	T cell suppression	T cell stimulation
	C/EBP family	

J Exp Med 2013; 210:2873

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