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IDO1 activity correlates with HGF levels and immune system impairment in multiple myeloma

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Presenter disclosure information

Sergio Rutella

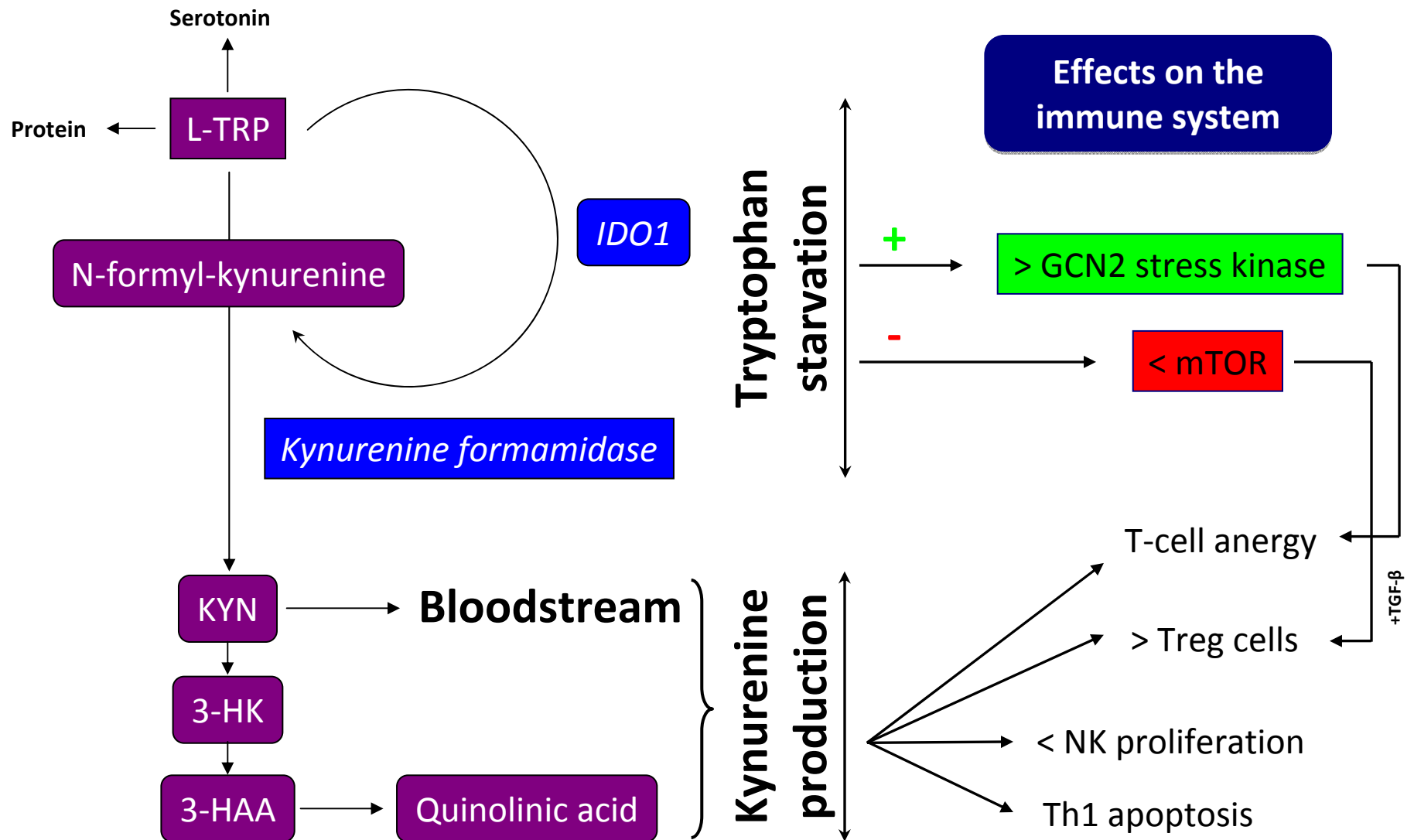
The following relationships exist related to this presentation:

No relationships to disclose

IDO1: Background

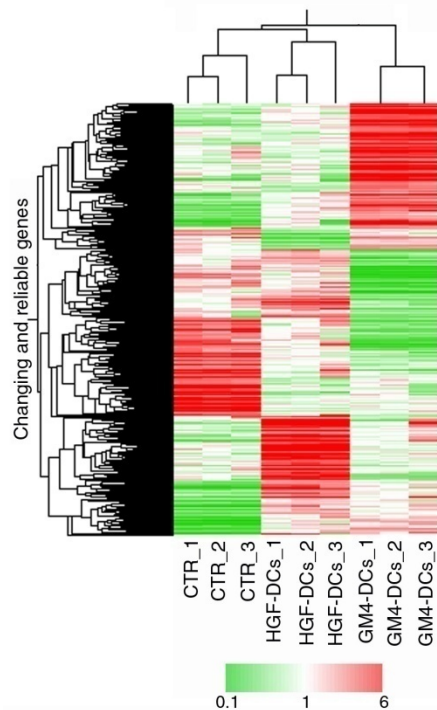
- Constitutively expressed by tumor cells and/or tumor environmental cells
- Induced by IFN- γ , a prototypical pro-inflammatory mediator
- Mediates tumoral immune escape
- Confers an unfavorable prognosis to certain tumor types (i.e., acute myeloid leukemia, ovarian cancer)
- Can be targeted with selective inhibitors (i.e., 1-methyl-tryptophan; INCB024360)

IDO1-driven TRP catabolism

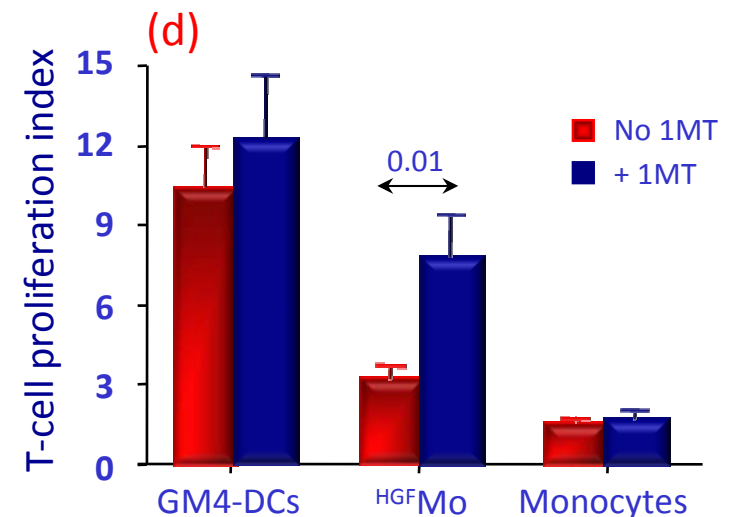
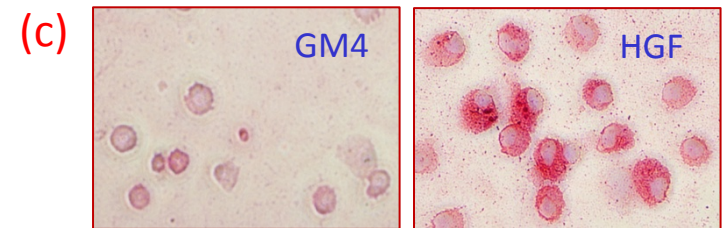
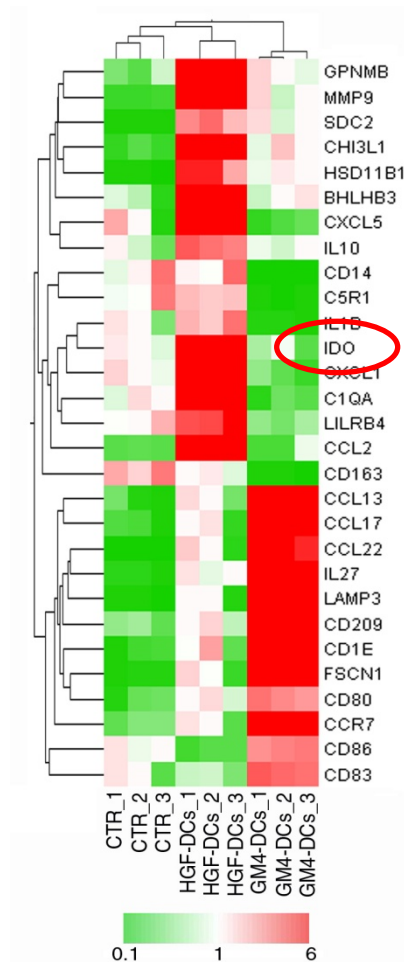


Hepatocyte growth factor (HGF) induces *IDO1* in human DC

(a) 672 significant probe sets up-regulated by HGF (ANOVA)



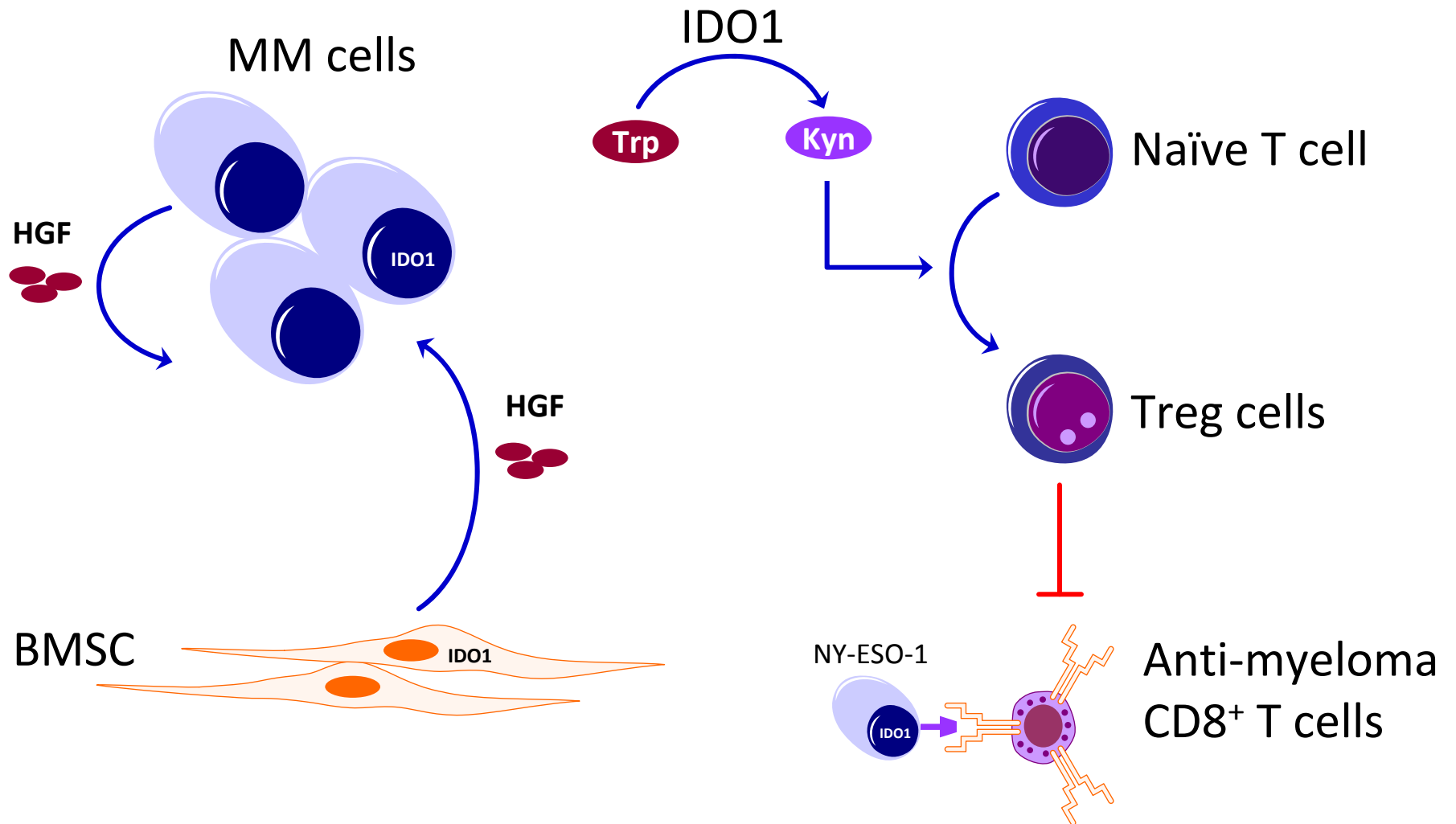
(b) 29 probe sets up-regulated by HGF (Tukey post-hoc test)



The immune defect in MM

- Infections are the leading cause of death
- DC are dysfunctional (IL-10⁺IL-12⁻CD80/86^{low})
- MM cells express CD28 and B7-coinhibitory molecules (PD-L1)
- Immune suppressive and angiogenic cytokines are increased (HGF, VEGF, IL-10, TGF- β)
- Treg cells are abnormal, both quantitatively and qualitatively
- Sensitivity to the graft-versus-myeloma effect indicates that the immune system is crucial to control the disease

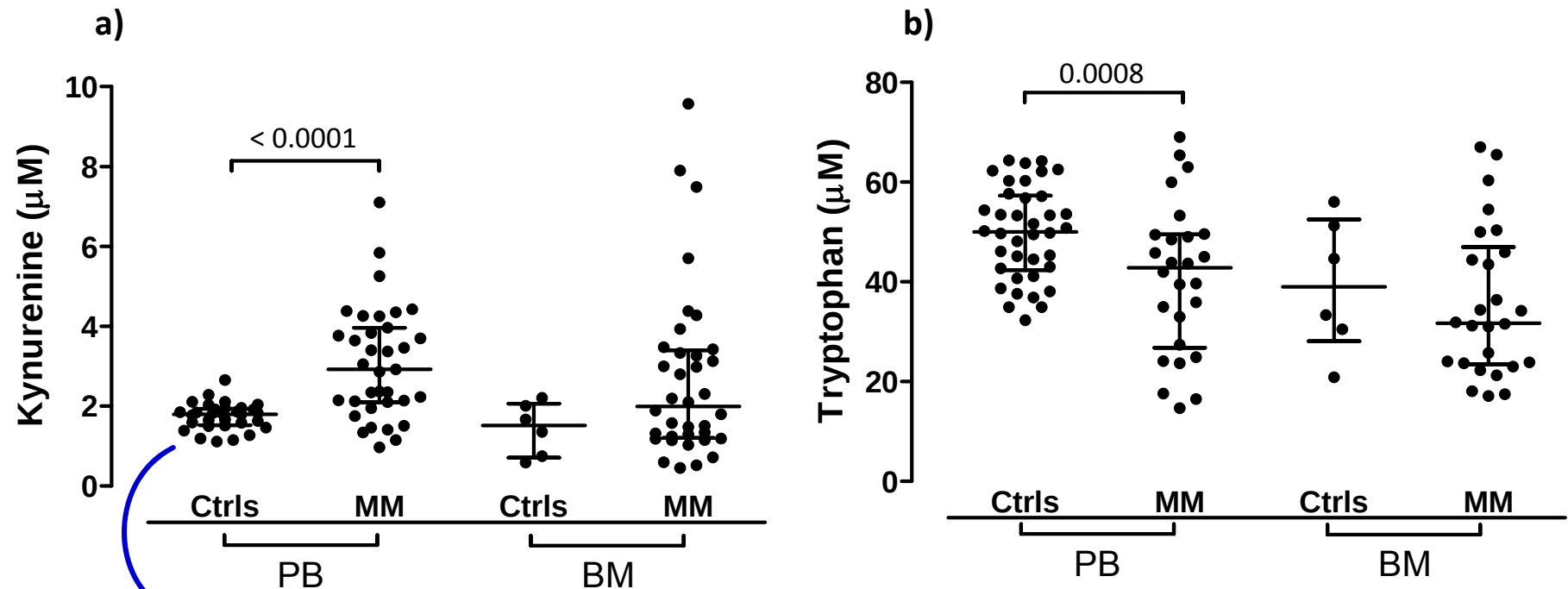
Study hypothesis



Patients

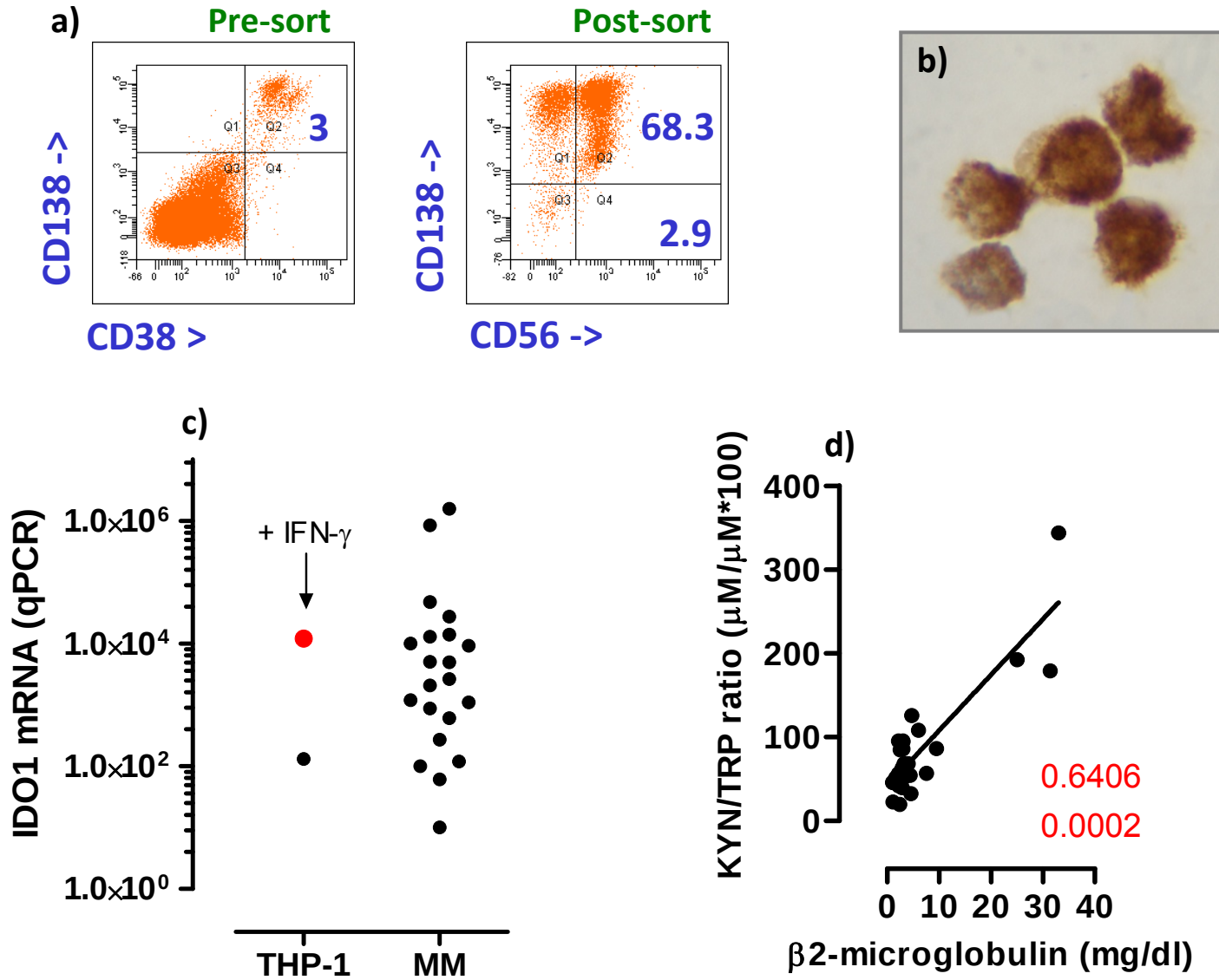
- 34 consecutive patients with PC dyscrasia
 - 27 symptomatic MM
 - 4 SMM
 - 3 MGUS
- 26 (77%) at disease onset / relapse
- 23 (67%) were not taking any medication at time of sampling
- β 2-microglobulin averaged 3.1 mg/dl (range 1.4-33.0)
- M-component averaged 2.6 g/dl (range 0.9-7.6)

KYN are increased in MM patients

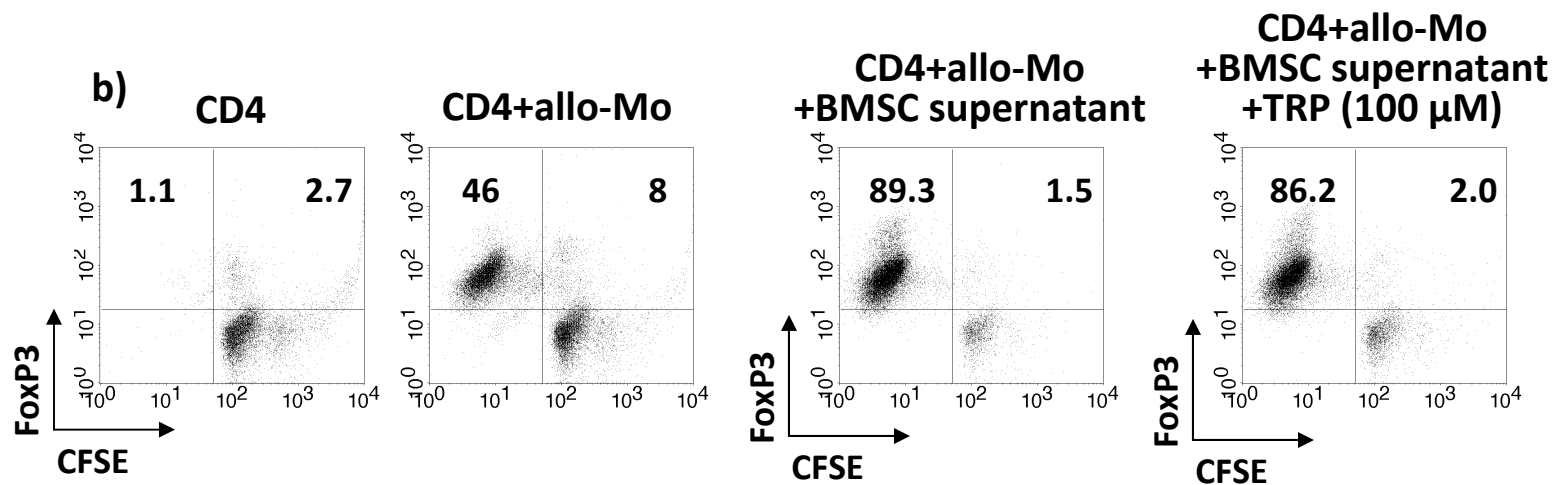
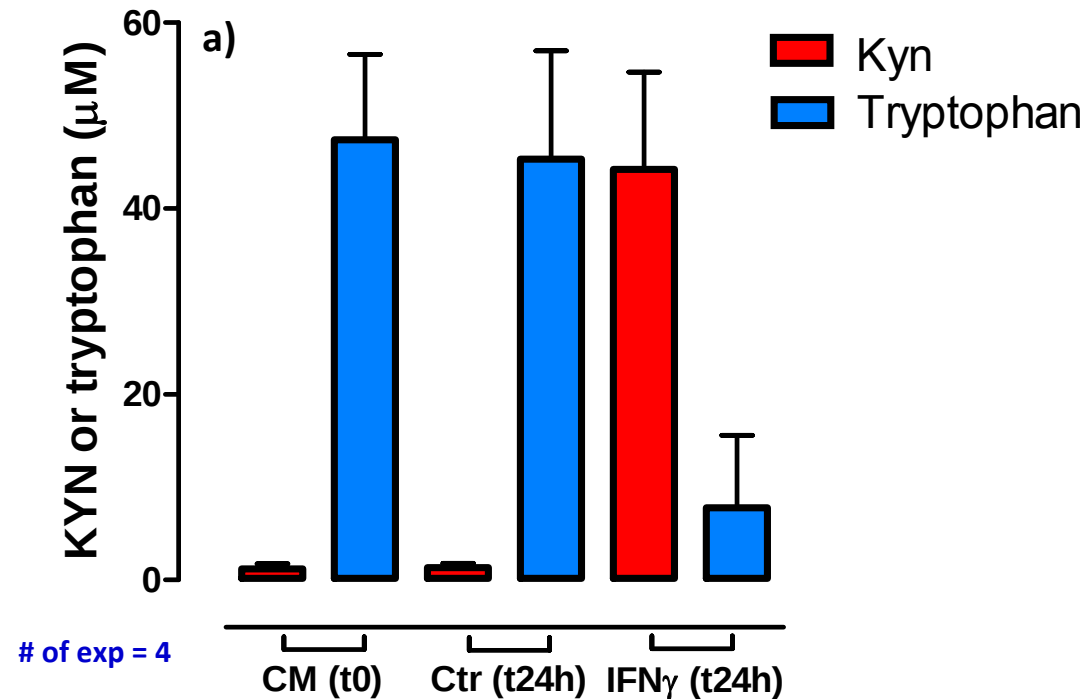


IDO⁻ MM < 1.8 $\mu\text{M/L}$ (8 pts, 23%)
IDO⁺ MM > 1.8 $\mu\text{M/L}$ (26 pts, 77%)

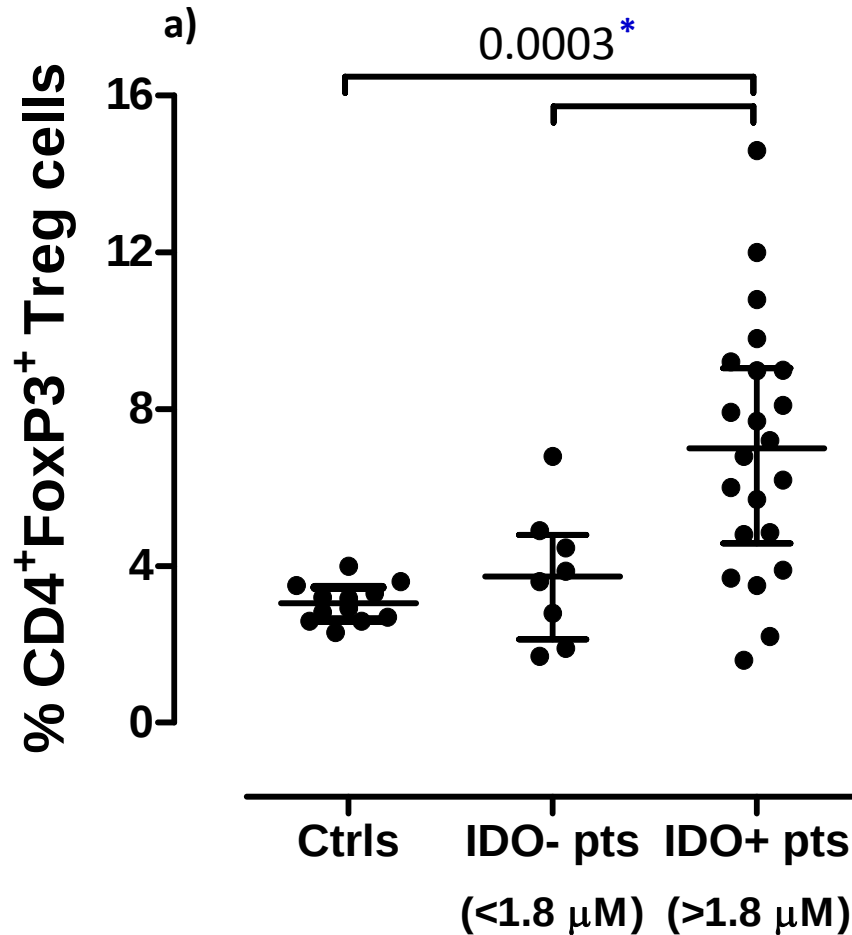
IDO1 is constitutively expressed by PC



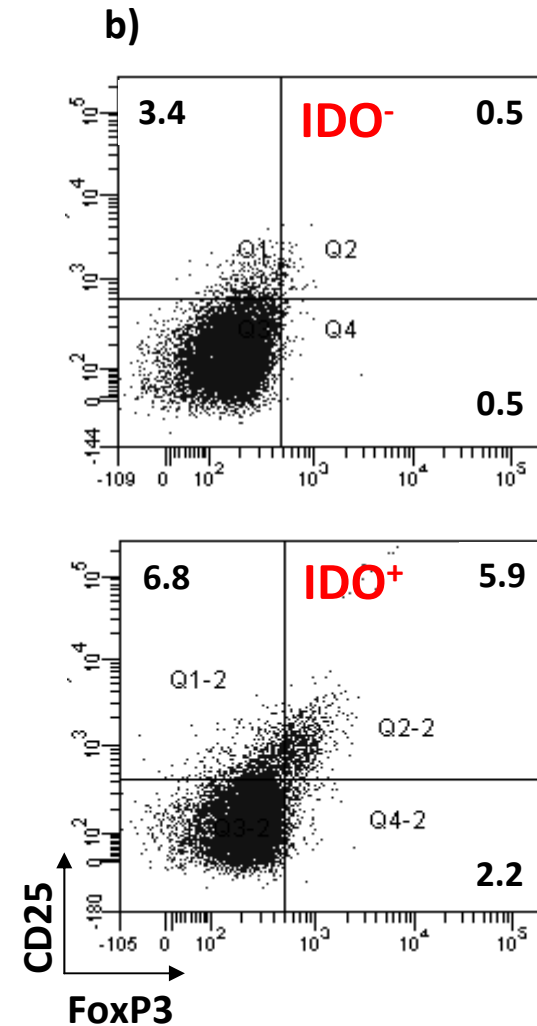
MM BMSC do not constitutively express IDO1



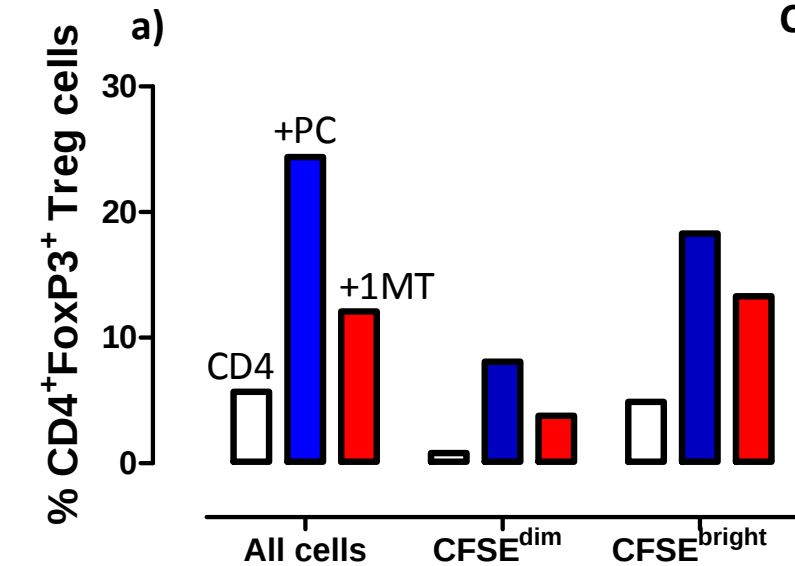
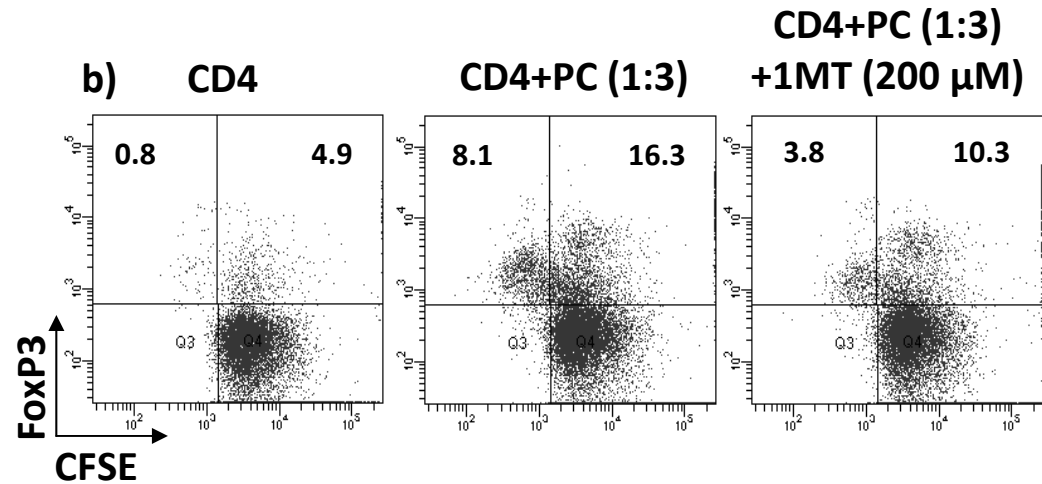
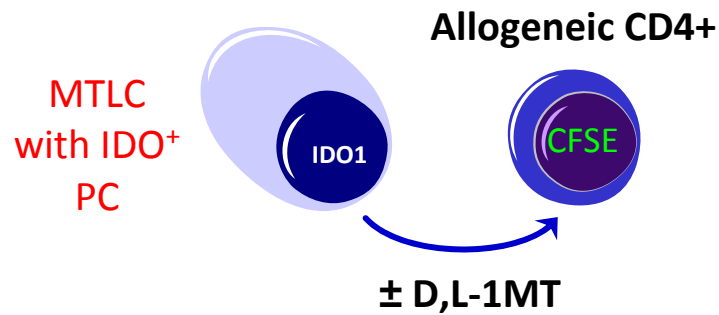
IDO1 may expand Treg cells *in vivo*



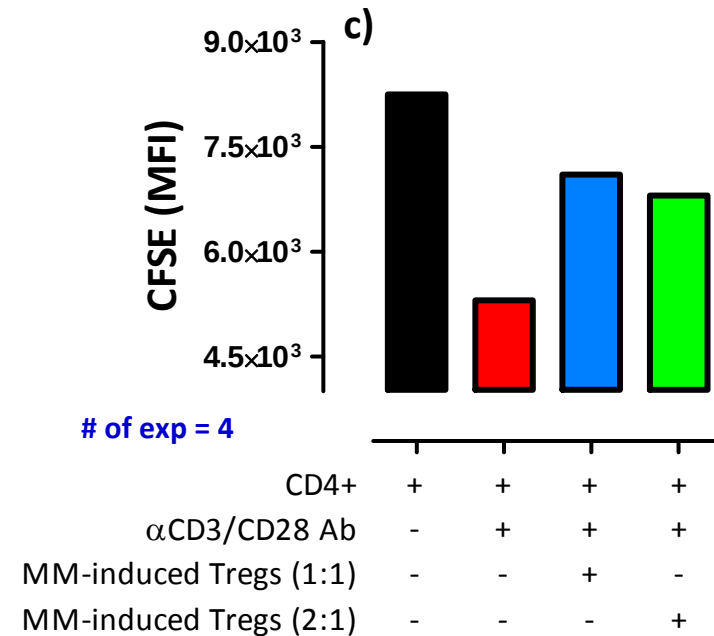
*By ANOVA



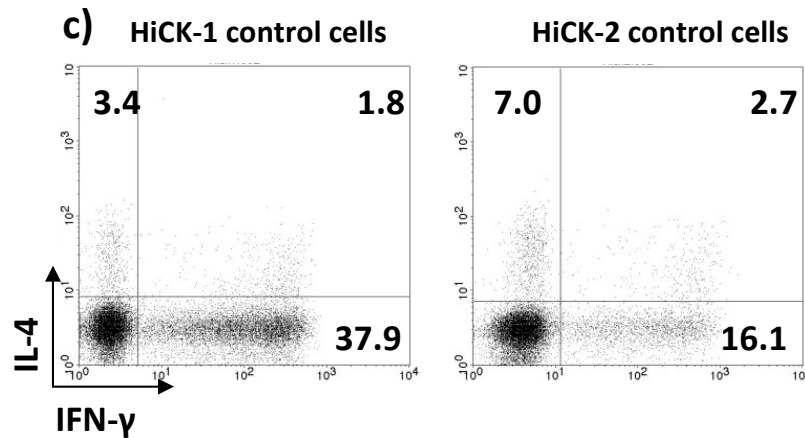
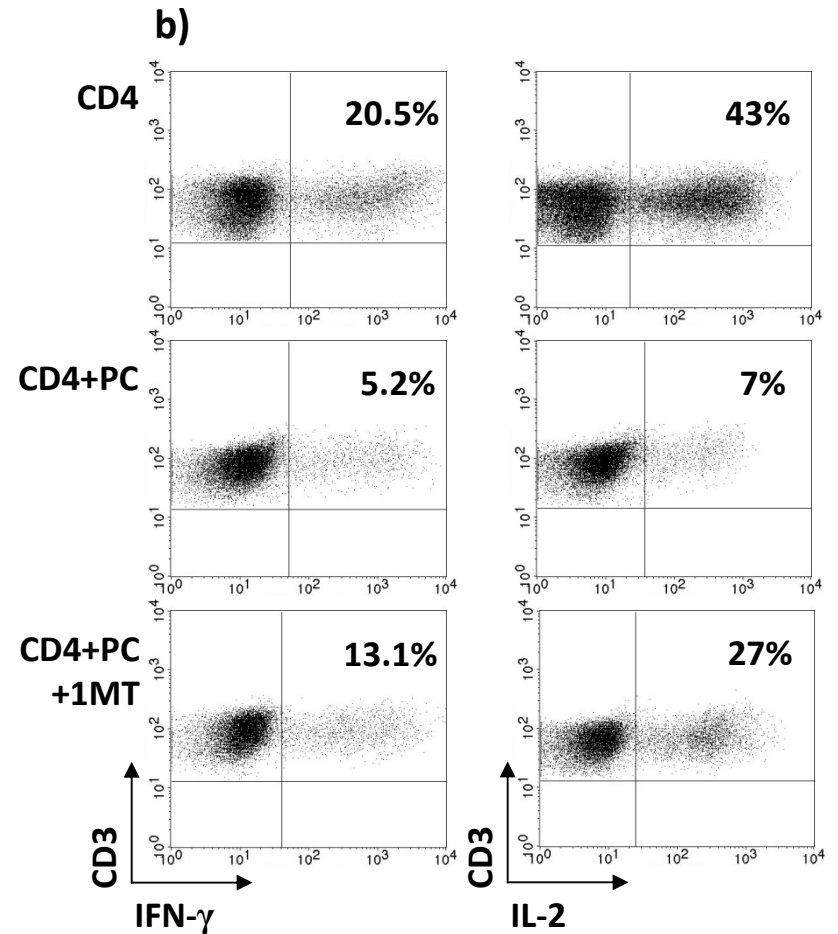
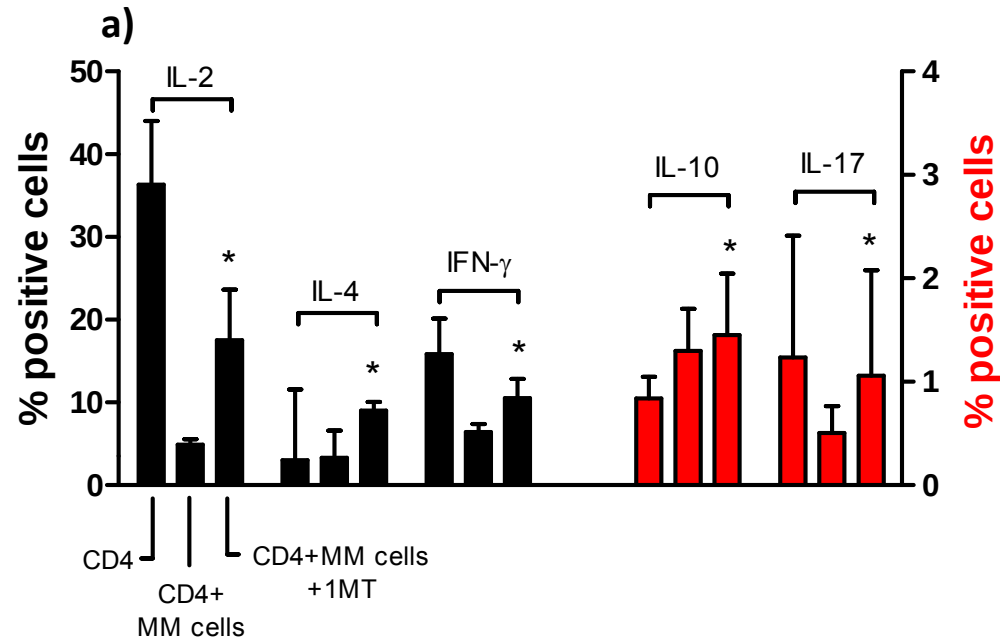
IDO1 induces Treg cells *in vitro*



of exp = 4



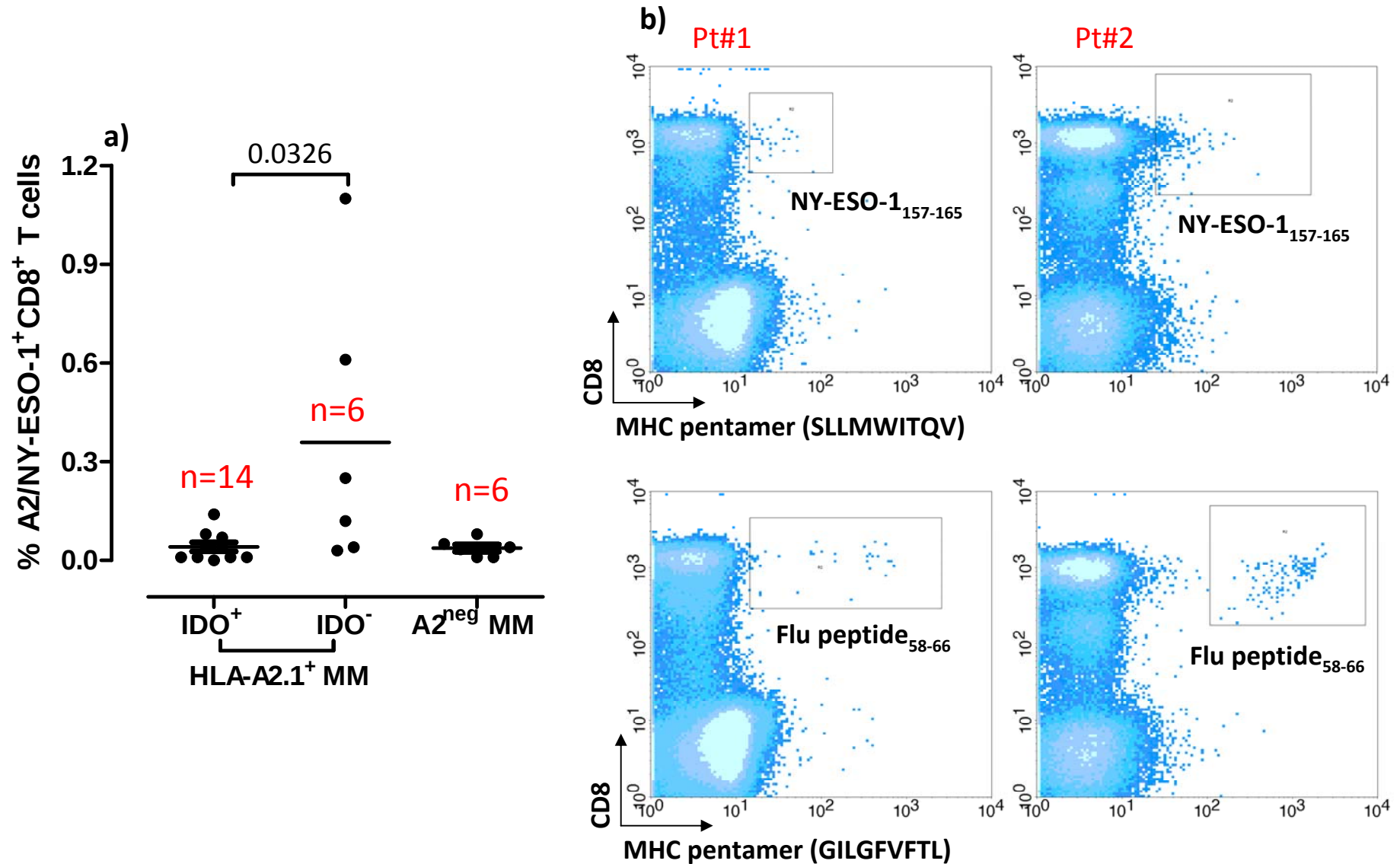
IDO1 restrains Th1/17 but not Th2 responses



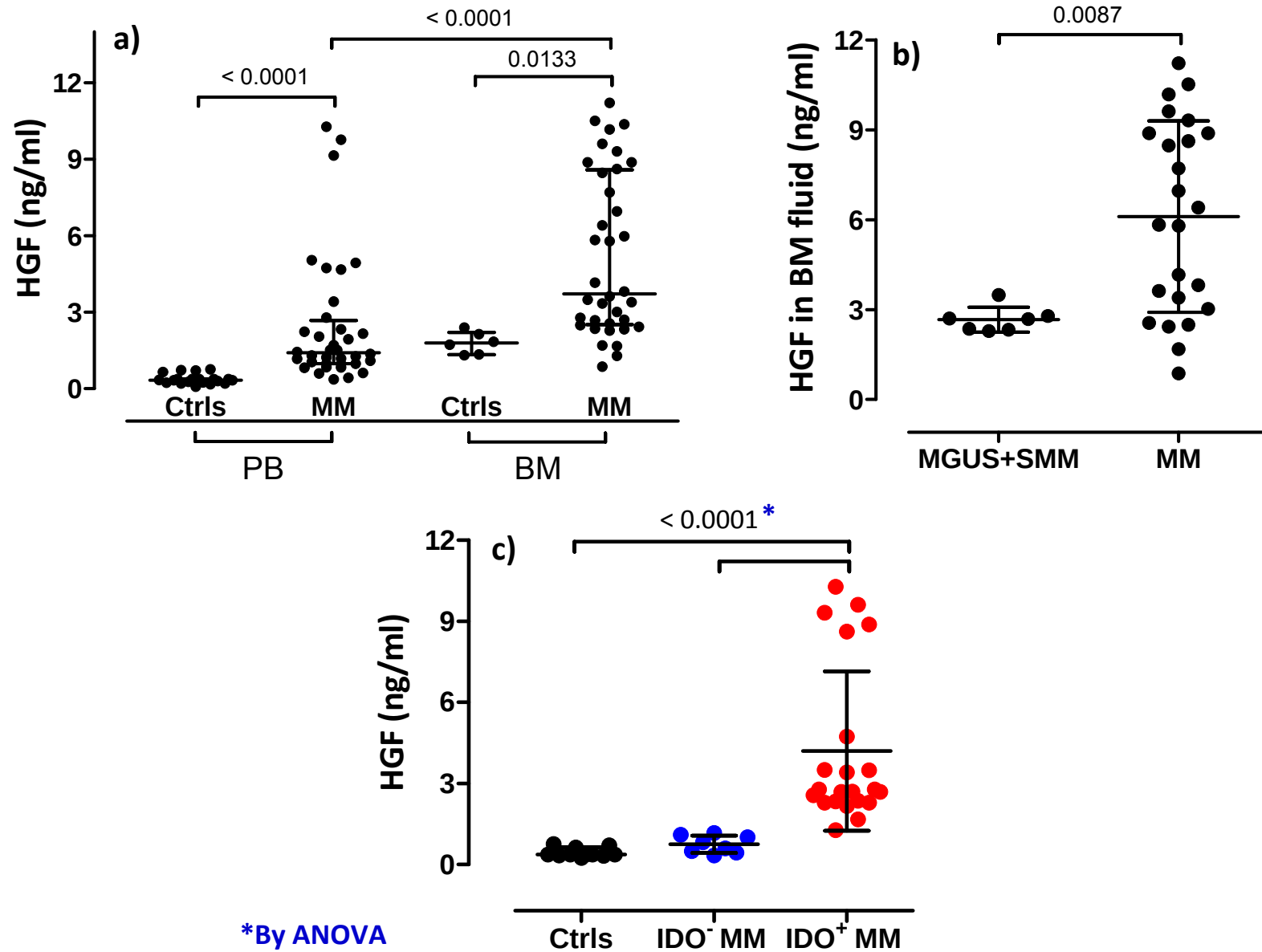
The NY-ESO-1 CT antigen

- A tumor-specific antigen (not expressed in normal tissues) and potential target of the graft-versus-MM effect
- Detected in 10-60% of MM (and in 100% of MM with cytogenetic abnormalities)
- T cells reactive against NY-ESO-1 account for 0.2-0.6% of CD8⁺ T cells in MM patients and can be detected with tetramers / pentamers in HLA-A2⁺ subjects

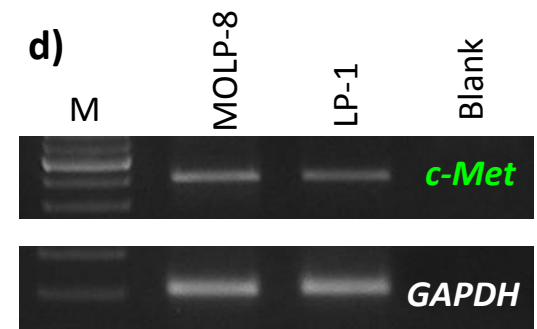
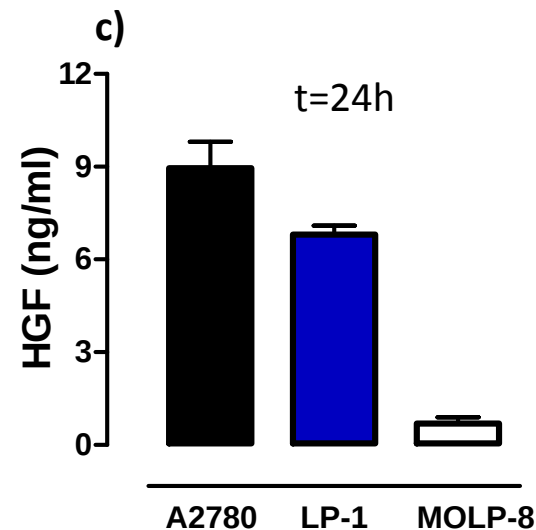
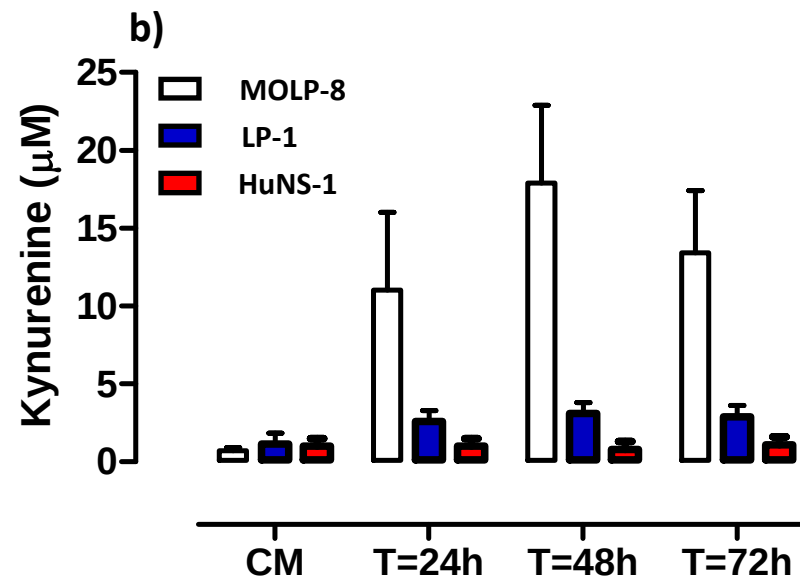
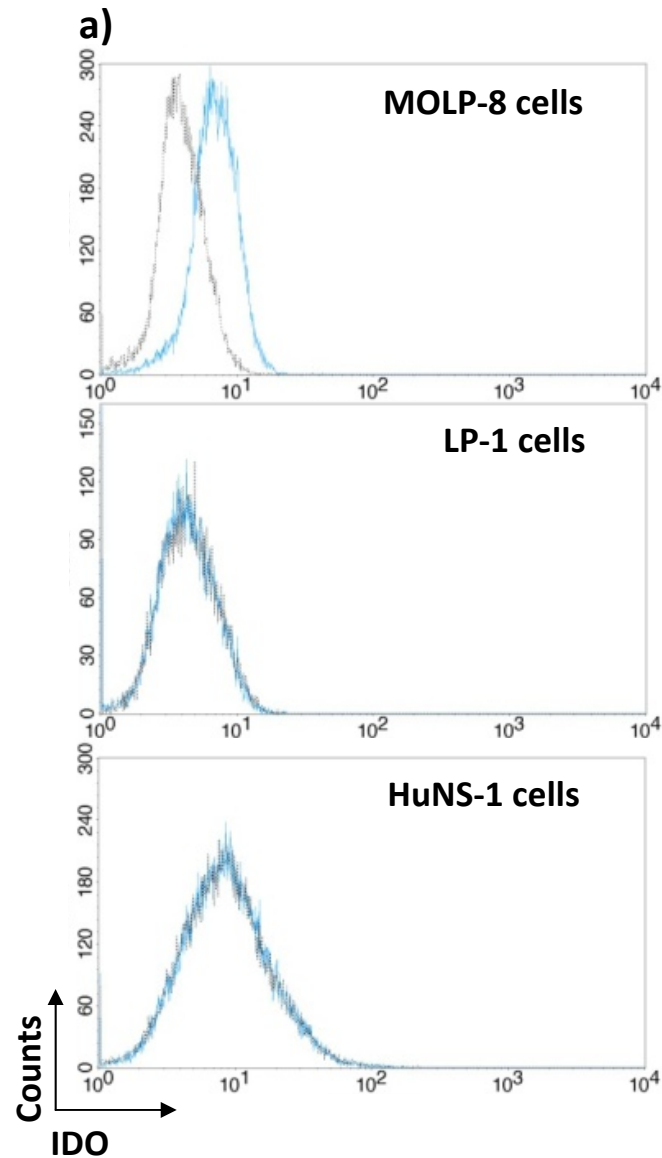
IDO1 restrains MM-reactive T cells



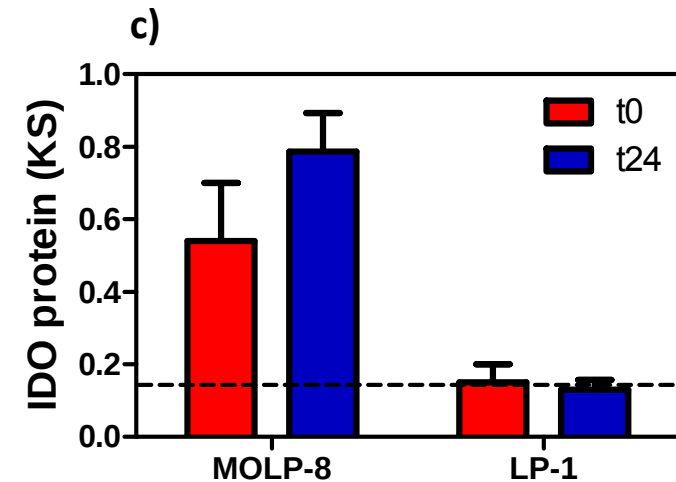
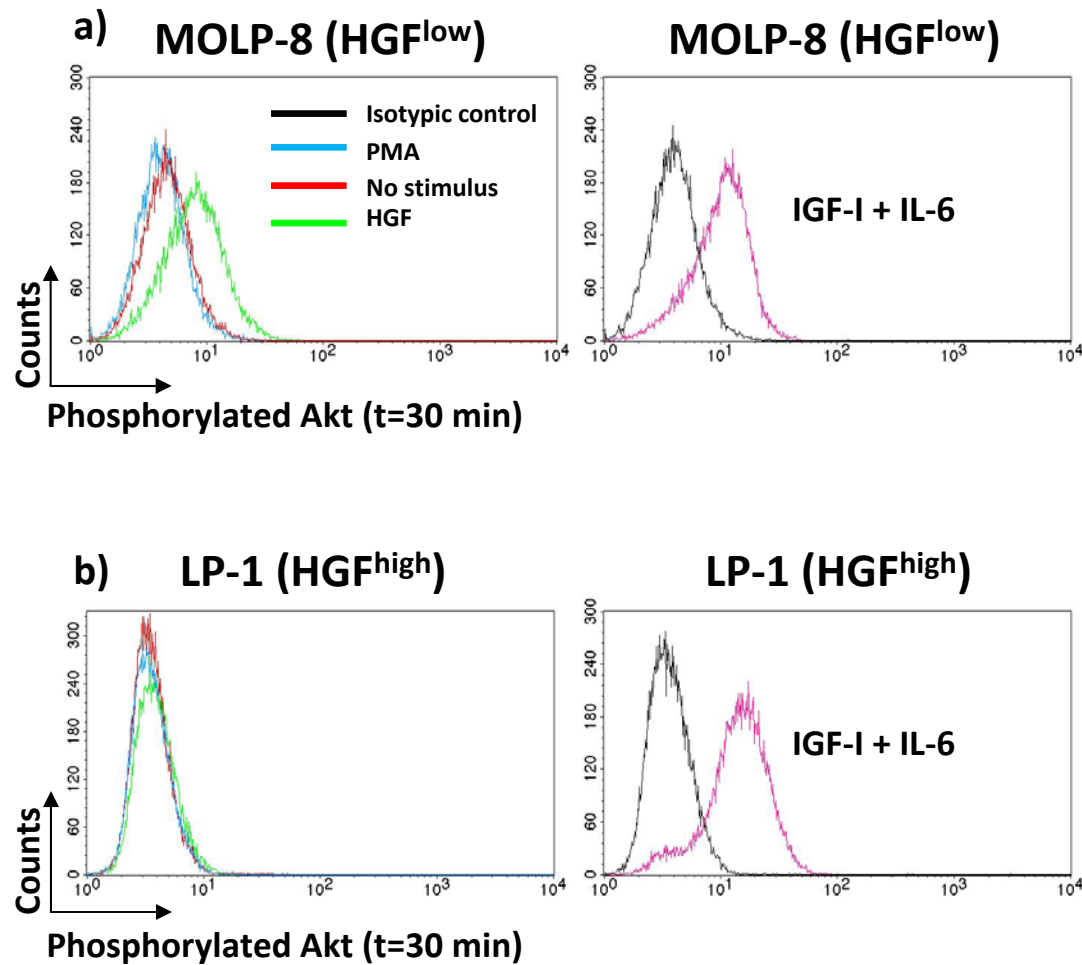
IDO1 activity correlates with HGF



IDO1 in MM cell lines



HGF induces IDO1 in HGF-sensitive MM cells



Conclusions

- IDO1 is expressed in MM
- IDO1 activity correlates with HGF release
- *Bona fide* Treg cells are increased and inversely correlate with myeloma-reactive T cells
- *In vitro*, IDO1 skews T-cell function towards a Th2/Treg cytokine secretion profile
- The HGF/IDO1 axis is a potential target of immune intervention in MM and other HGF-secreting tumors

Acknowledgments

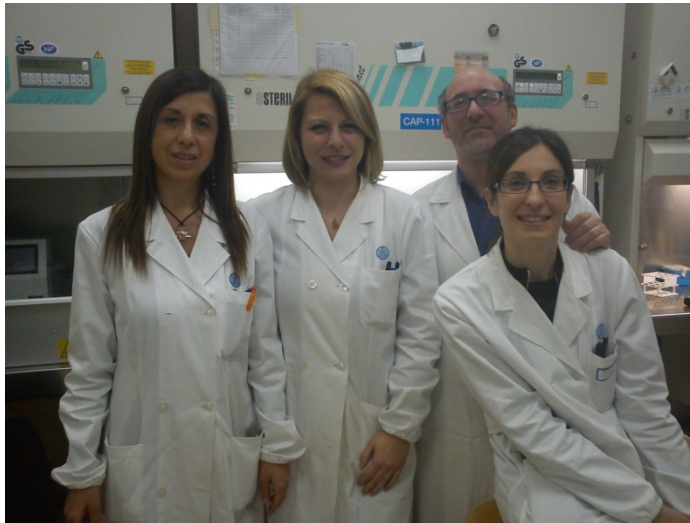
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Con la ricerca, contro il cancro.



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