SITC 2018

NOVEMBER 7-11
WASHINGTON, D.C.
Walter E. Washington
Convention Center

sitc
Society for Immunotherapy of Cancer

Regulation of Myeloid-Derived Suppressor Cells in Cancer

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The Wistar Institute, Philadelphia, PA, USA

1894

2014

Presenter Disclosure Information

Dmitry Gabrilovich

I have the following financial relationships to disclose:

Consultant for: Merck, Quentis, T-Rx Pharmaceuticals, Shattuck Lab, Nilogen, Infinity

Grant/Research support from: Bristol-Myers Squibb, Janssen, Syndax

- and -

I will not discuss off label use and/or investigational use in my presentation.

Strong activation signal. Short duration

Monocytes and mature neutrophils mobilization from bone marrow

Main trigger -TLR

Activated phagocytosis
Respiratory burst
Pro-inflammatory cytokines
Up-regulation of co-stimulatory molecules

Elimination of threat (killing pathogens)
Activation of adaptive immunity

Weak activation signal mostly growth factors and cytokines. Long duration

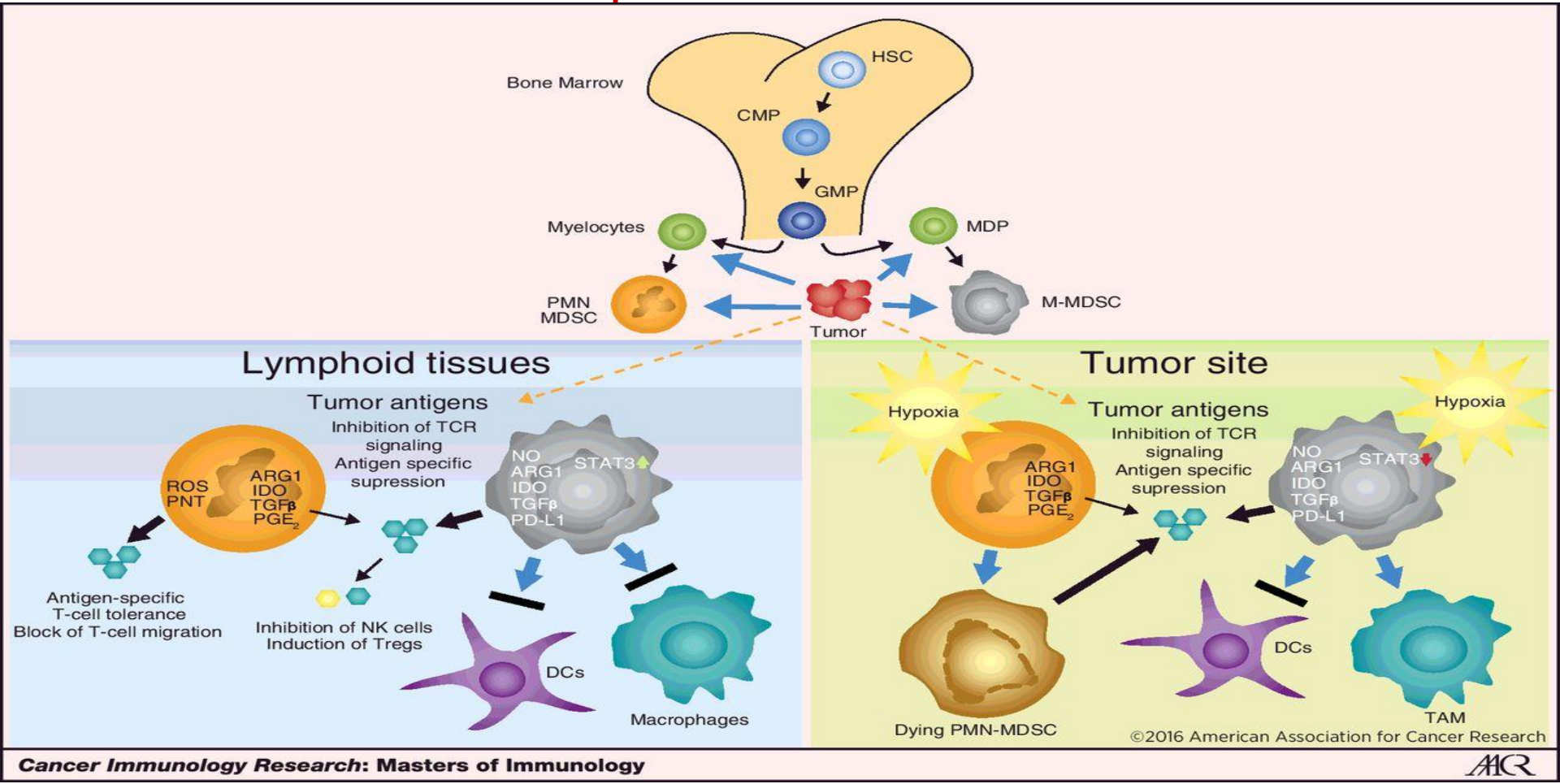
Mild but prolong production of monocytes and neutrophils

Main trigger – pro-inflammatory cytokines and ER stress response

Weak phagocytosis
Constant production of ROS and NO
Anti-inflammatory cytokines
Arginase, PGE2

Inhibition of adaptive immunity
“Pathologic tissue remodeling” leading to metastases

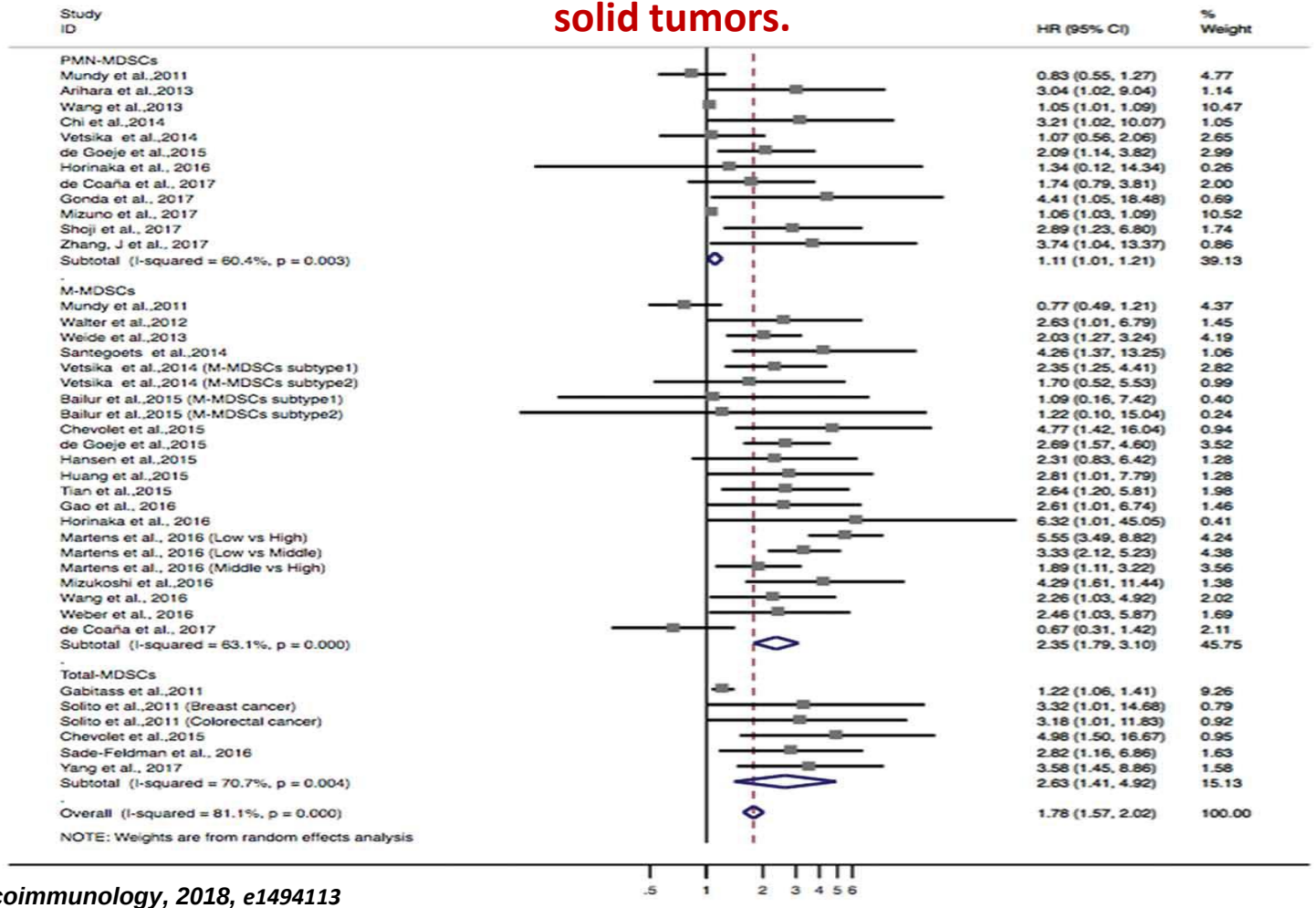
Development and function of MDSCs



Cancer Immunology Research: Masters of Immunology

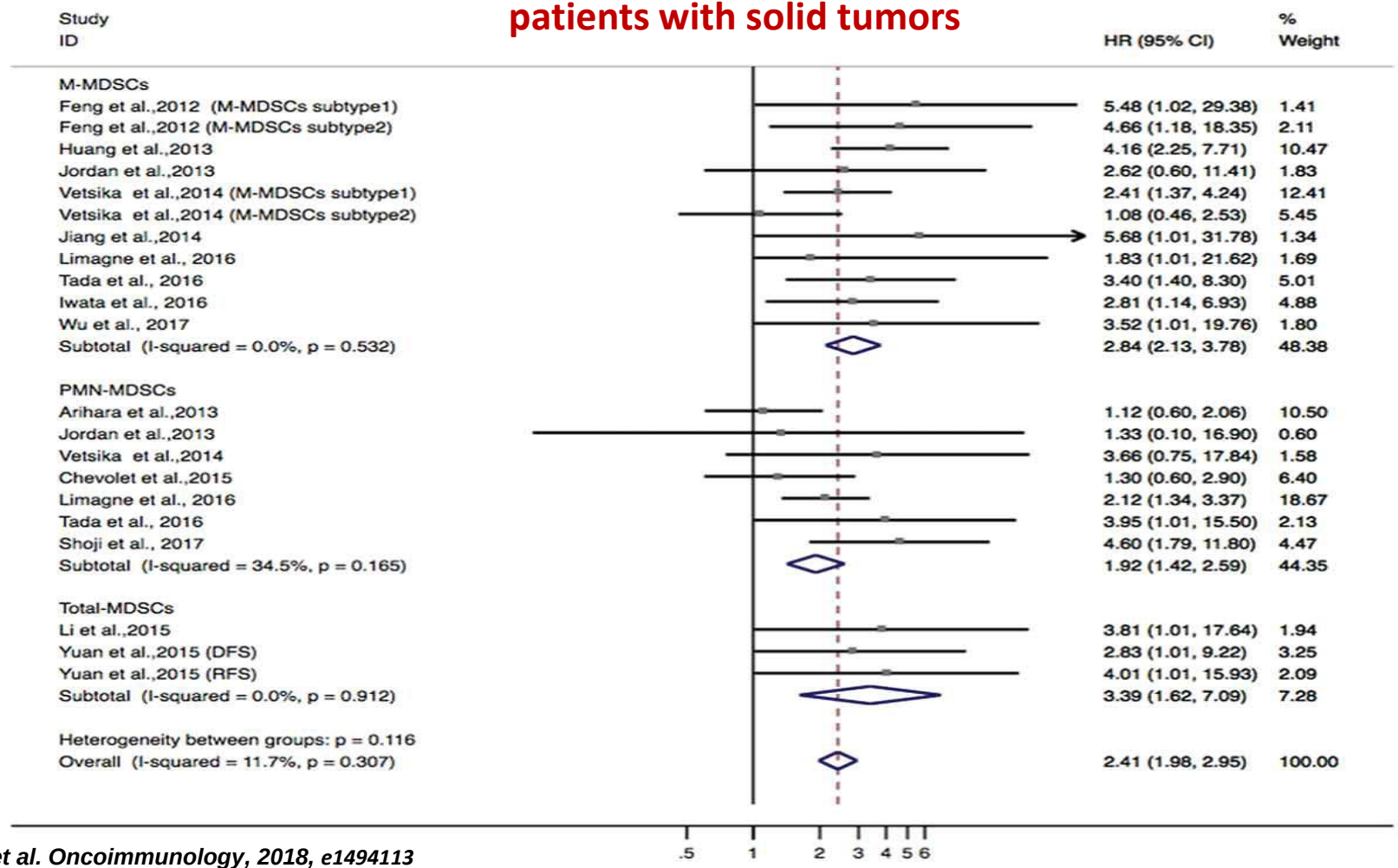
Dmitry I. Gabrilovich Cancer Immunol Res 2017;5:3-8

Meta-analysis of the association between different types of MDSCs and OS in patients with solid tumors.

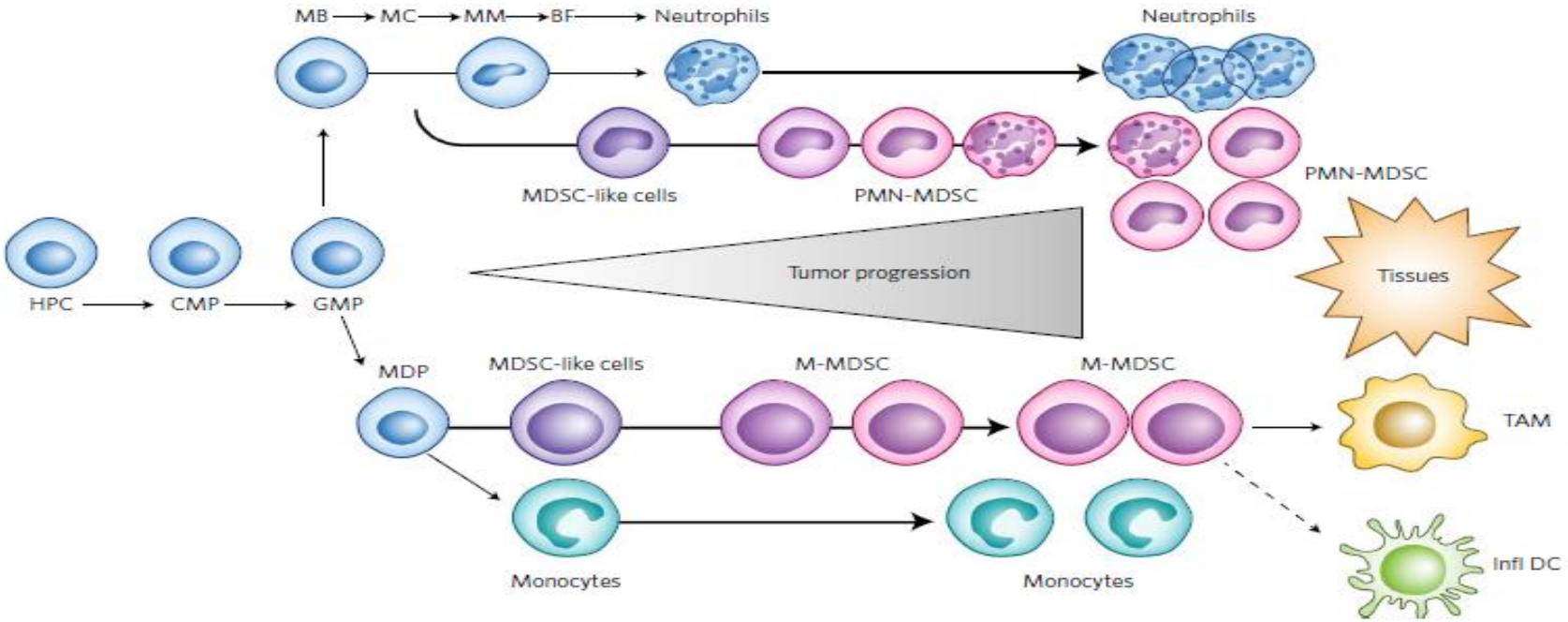


Wang et al. Oncoimmunology, 2018, e1494113

Meta-analysis of the association between different types of MDSCs and DFS/PFS/RFS in patients with solid tumors



Wang et al. Oncoimmunology, 2018, e1494113



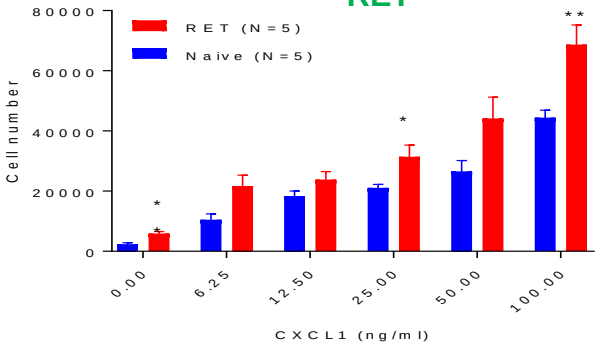
Veglia F et al. Nat Immunol. 2018

Chemotaxis of bone marrow neutrophils from GEM

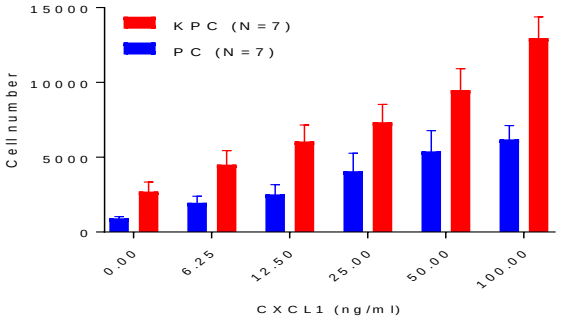
CXCL1

Cell number

RET



KPC



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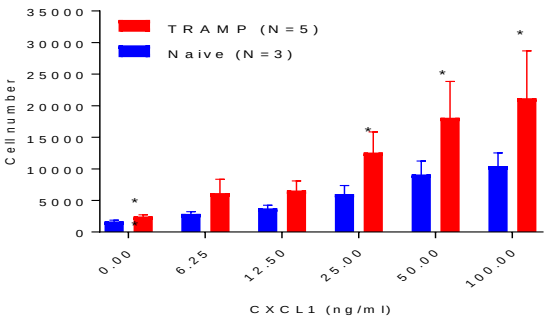

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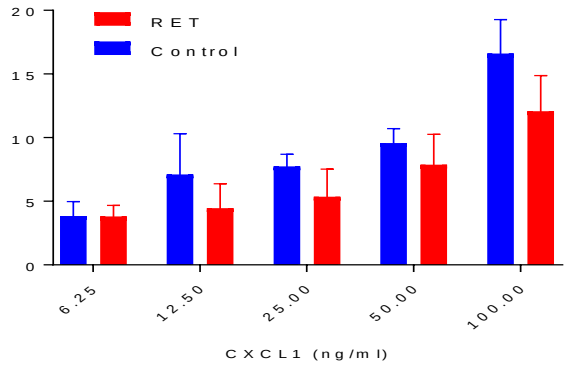

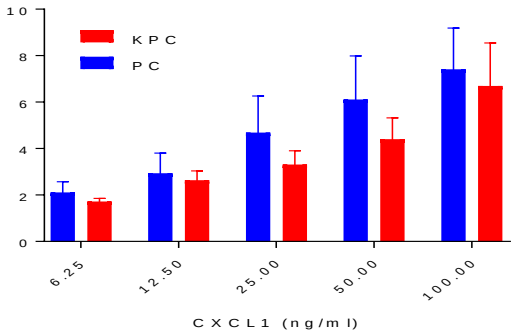

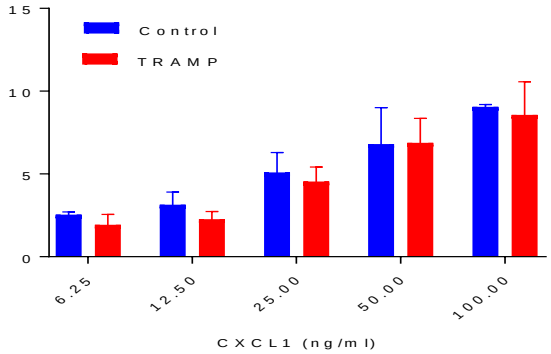

fMLP

Cell number

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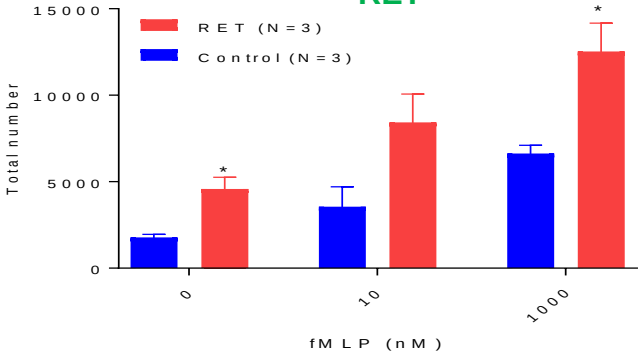

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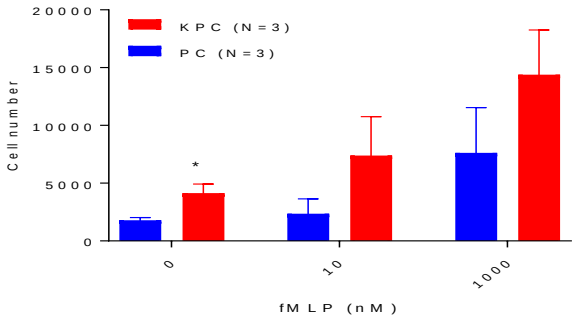

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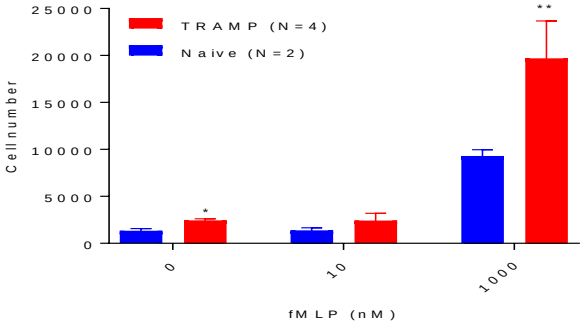
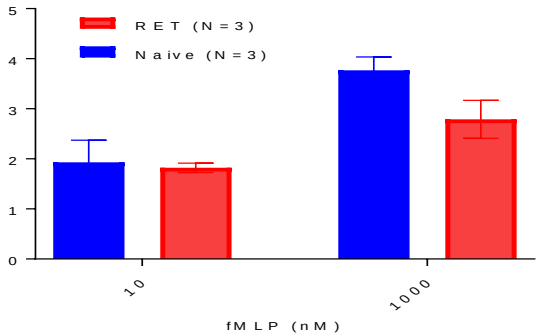
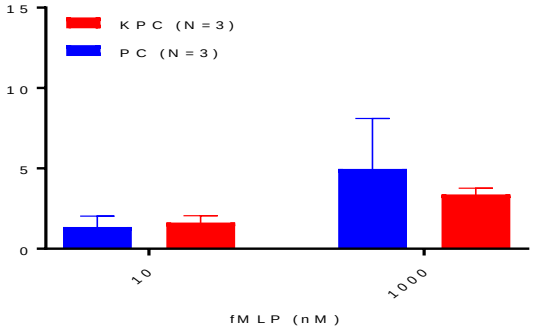
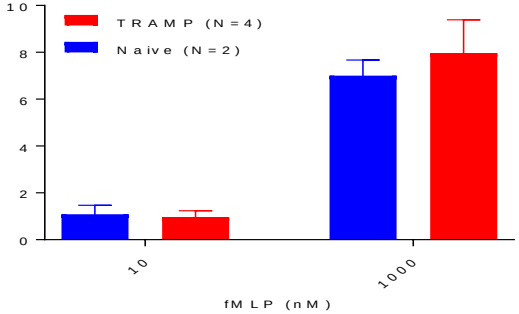


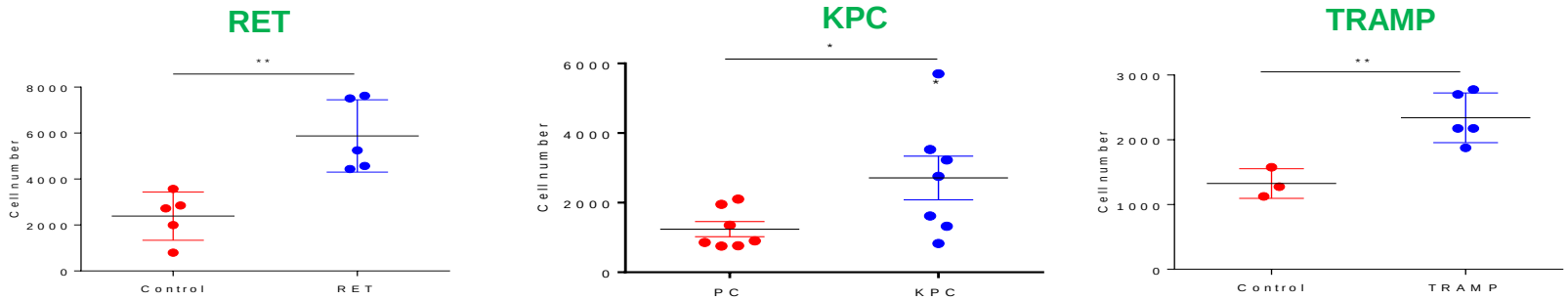
Fold increase



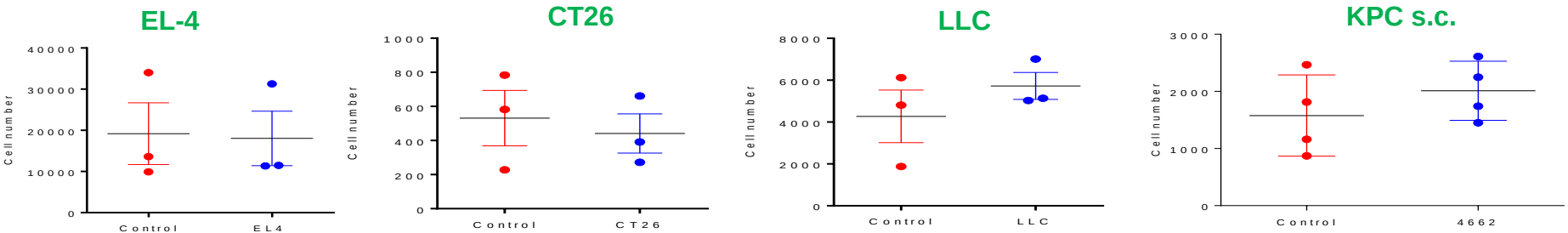




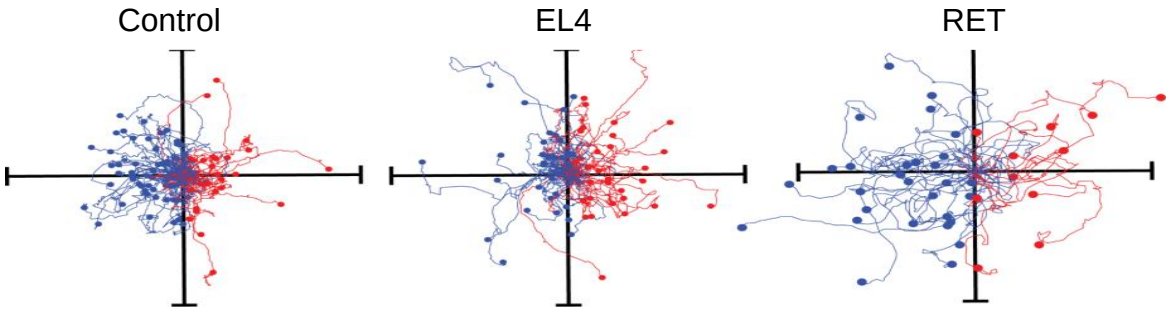
Spontaneous migration of bone marrow neutrophils from GEM



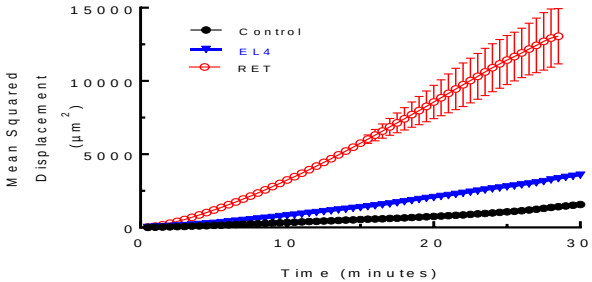
Spontaneous migration of bone marrow neutrophils from transplantable models



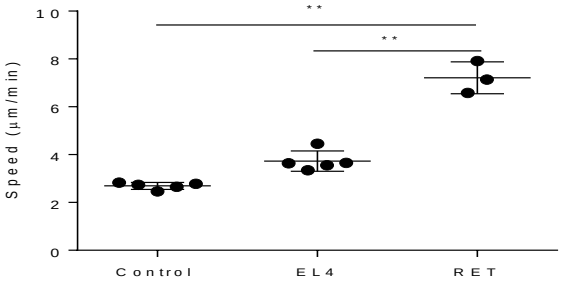
Migration of bone marrow neutrophils



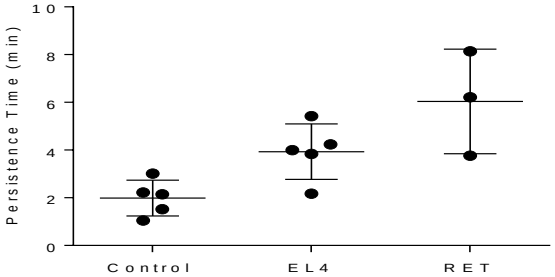
Mean square displacement



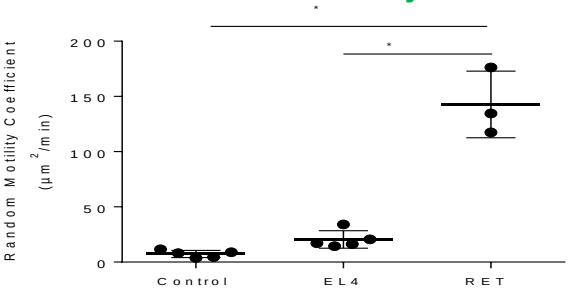
Speed



Persistence time

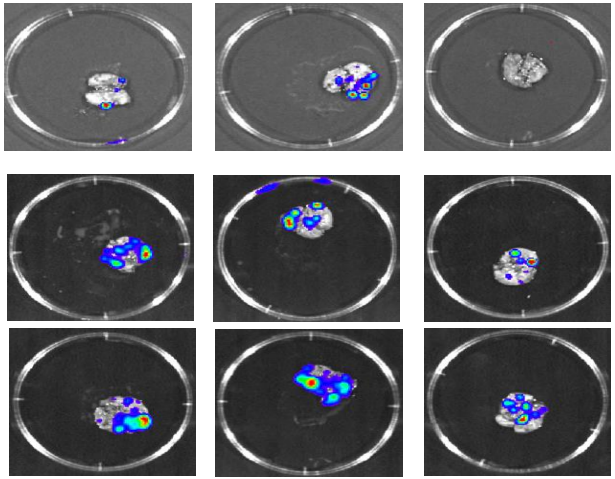


Random motility coeffic.



Migration of bone marrow neutrophils depends on tumor stage

Orthotopic LL2

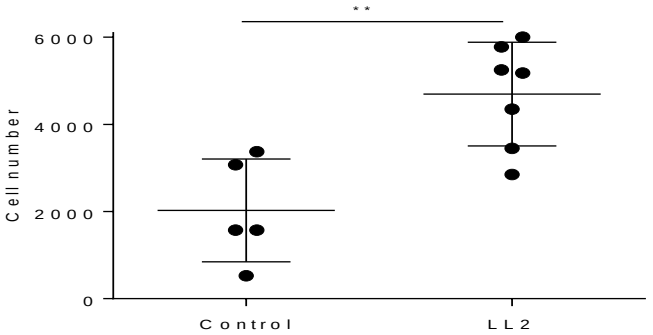


Week 1

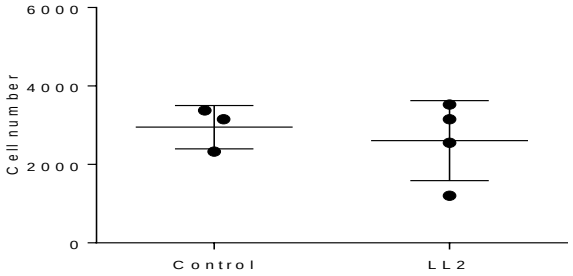
Week 2

Week 3

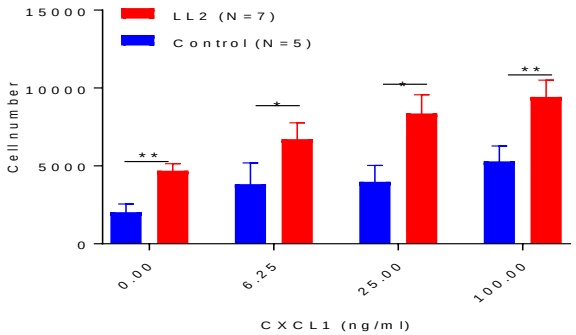
One week



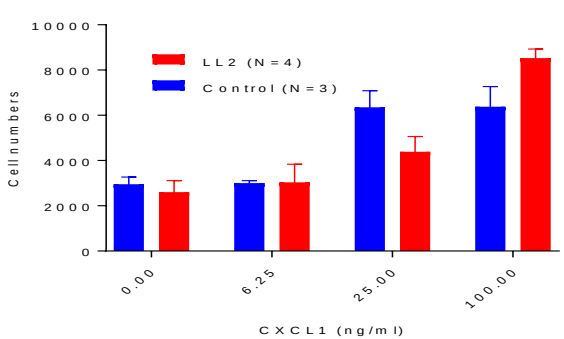
Three weeks



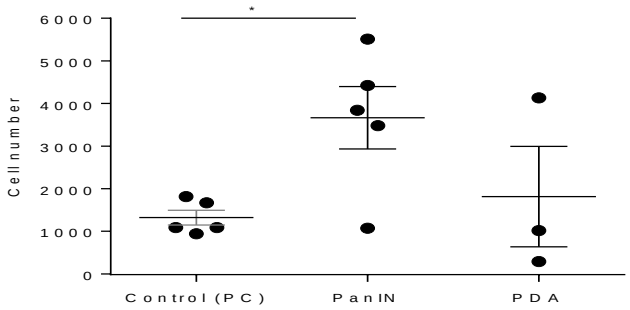
One week



Three weeks



KPC GEM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5000
4000
3000
2000
1000
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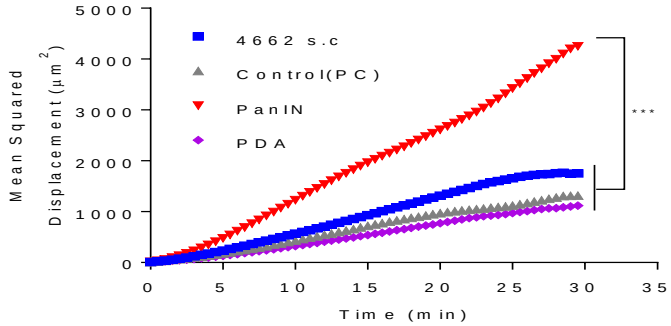
Control (PC)
PanIN
PDA


Mean Squared Displacement (μm²)
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4000
3000
2000
1000
0
4662 s.c
Control(PC)
PanIN
PDA
***
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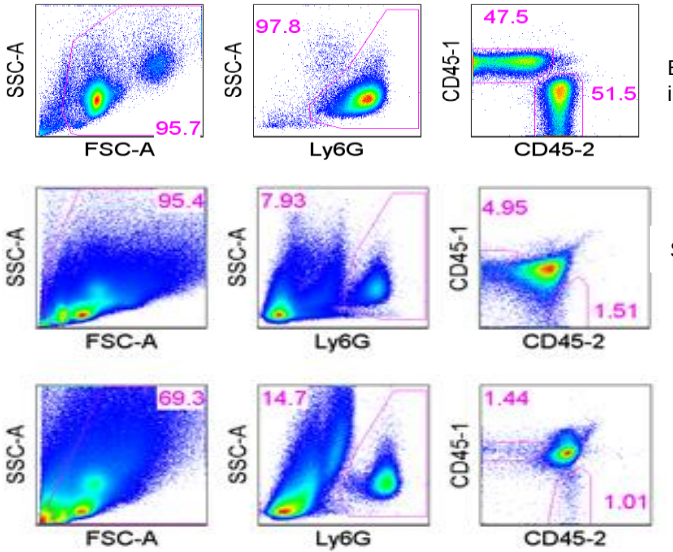
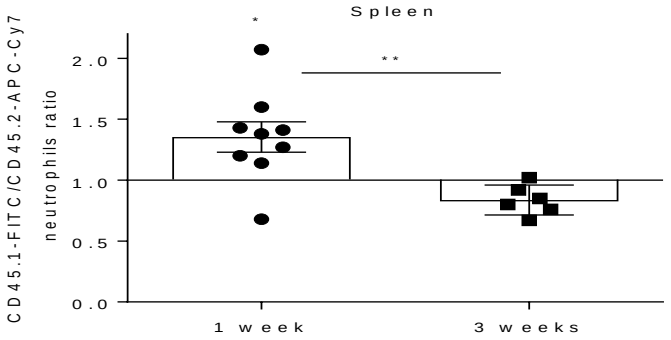
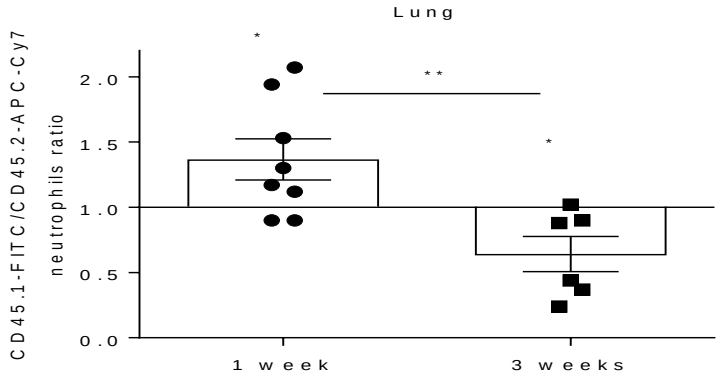
15
20
25
30
35
Time (min)

Migration of bone marrow neutrophils *in vivo*

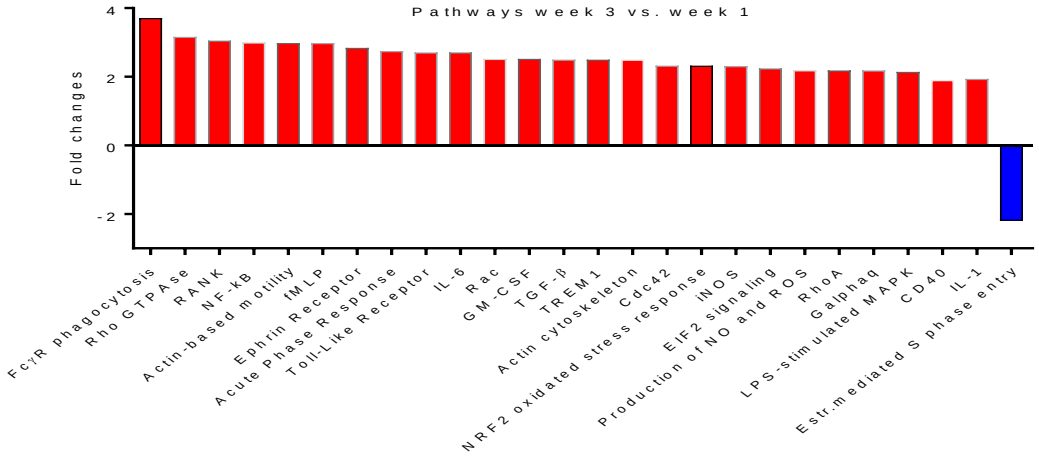




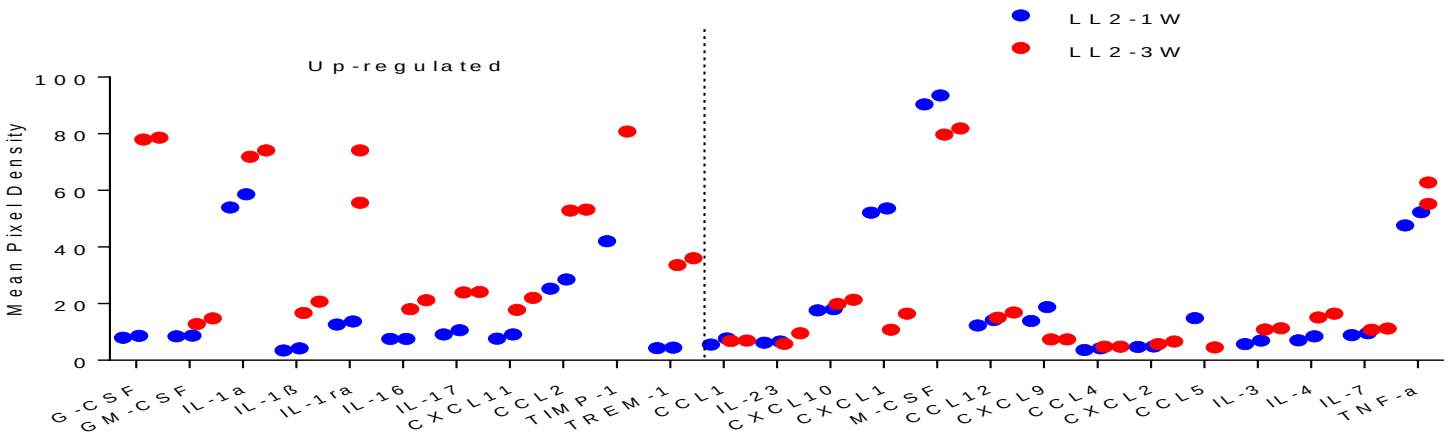


Inflammation is a feature of BM neutrophils from advanced stage tumors

RNAseq

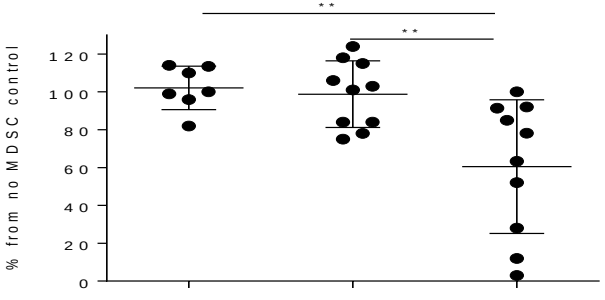


Cytokine array

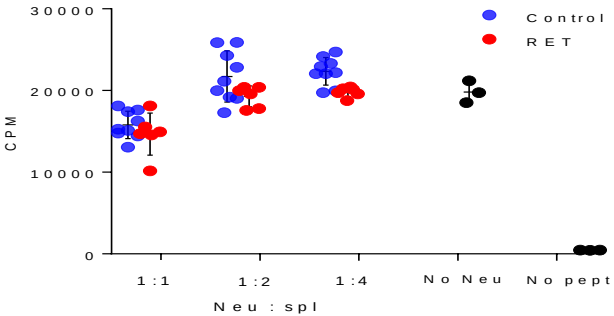


Immune suppression of BM neutrophils

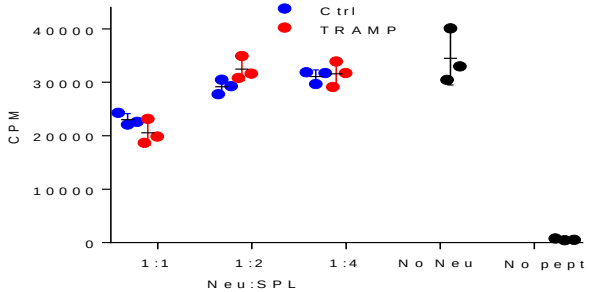
Orthotopic LL2



RET GEM



TRAMP GEM



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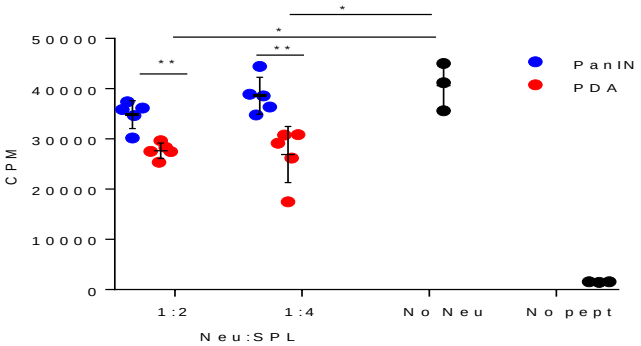
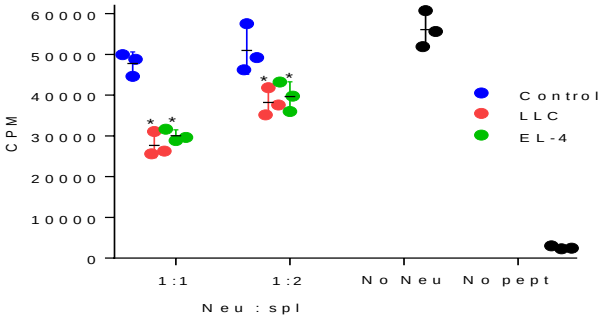
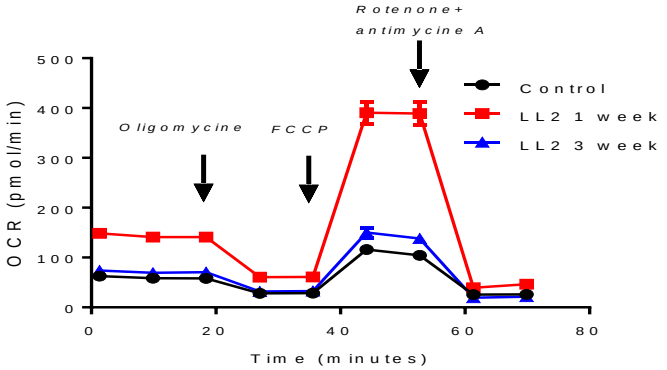


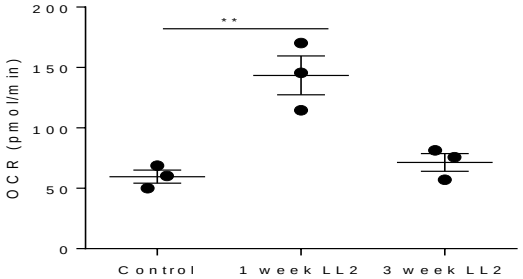
Transplantable s.c. tumors

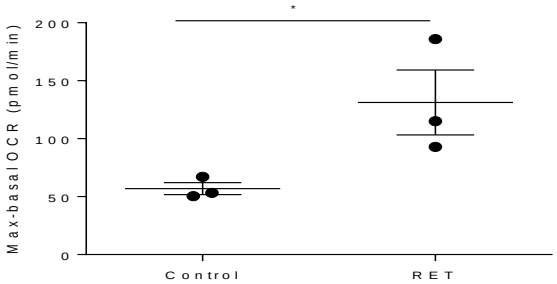


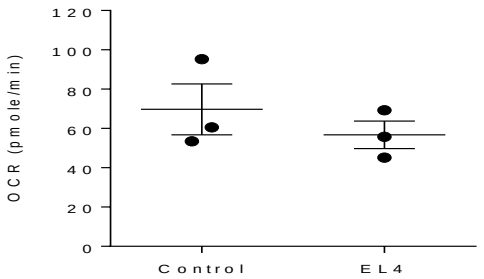
Metabolism of BM neutrophils
Oxidative phosphorylation and glycolysis



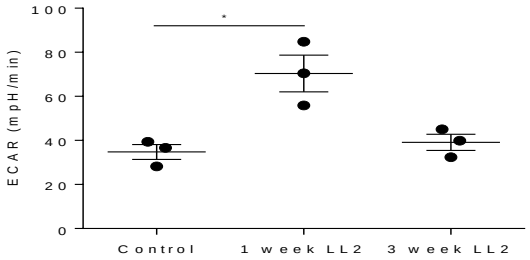
Oxygen Consumption Rate - OCR

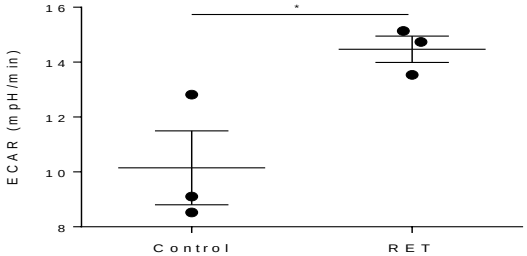


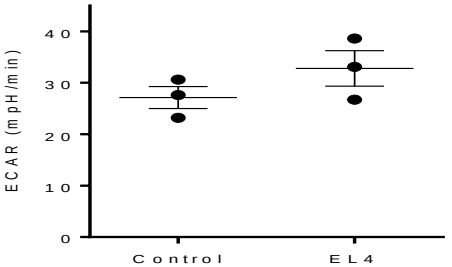




Extracellular Acidification Rate - ECAR

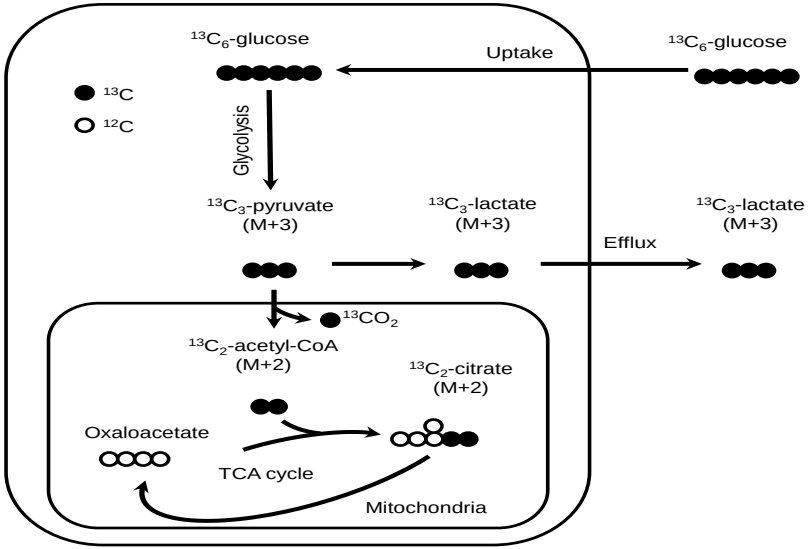


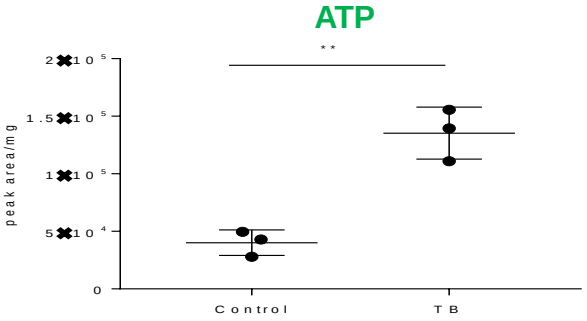


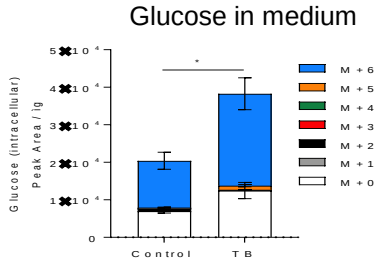


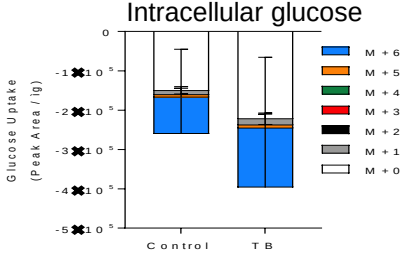
Metabolism of BM neutrophils

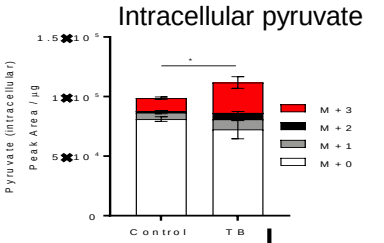
TCA cycle RET mice

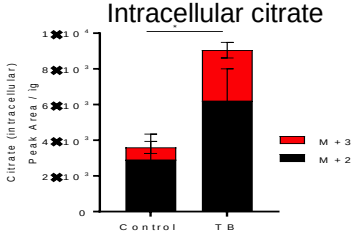


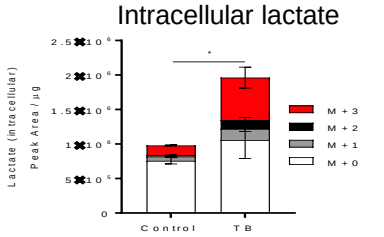


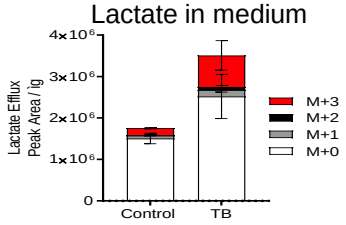








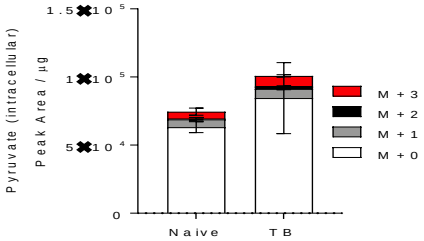




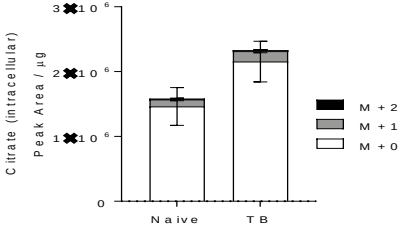
Metabolism of BM neutrophils

TCA cycle LL2 mice (3 weeks)

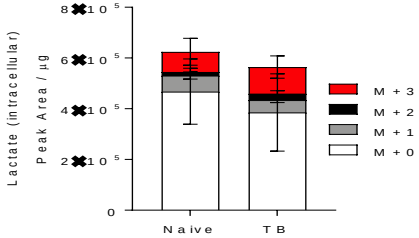
Intracellular pyruvate



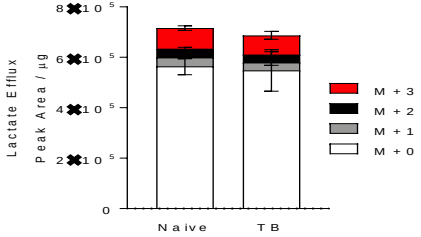
Intracellular citrate



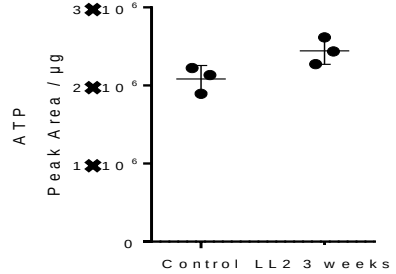
Intracellular lactate



Lactate in medium

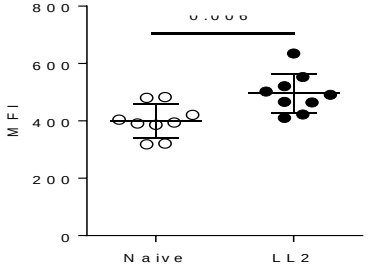


ATP

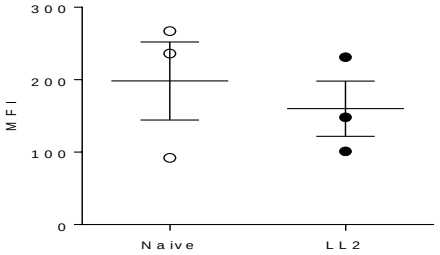


Glut1 expression

One-week LL2

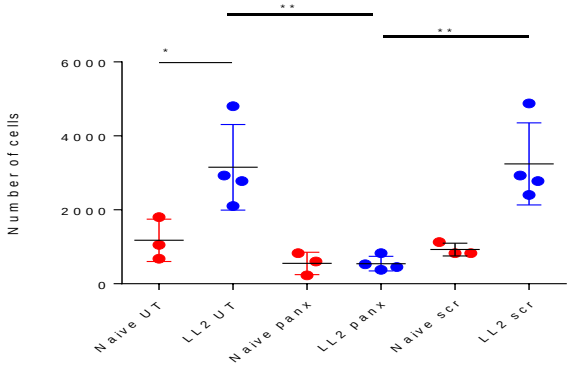


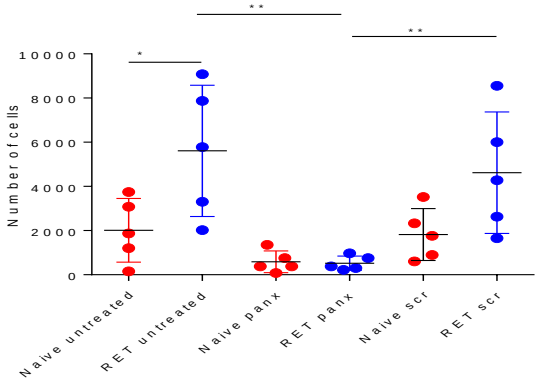
One-week LL2



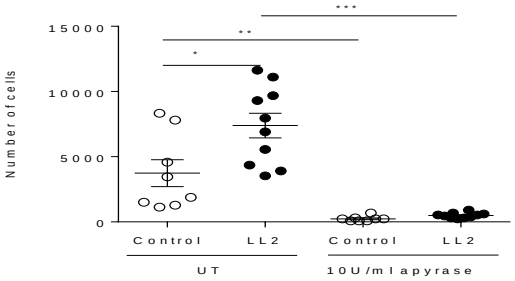
ATP mediated migration of BM neutrophils

Inhibition of ATP release from cells

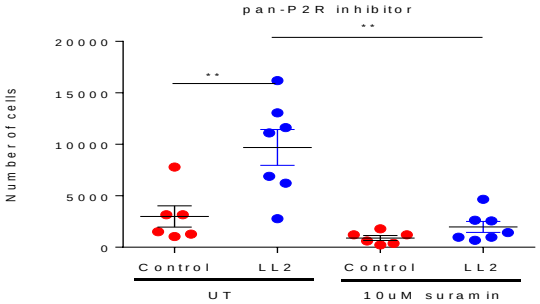


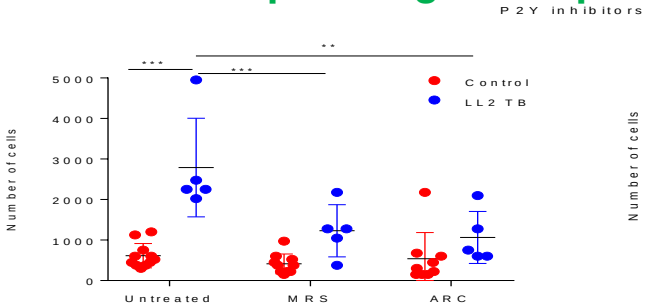


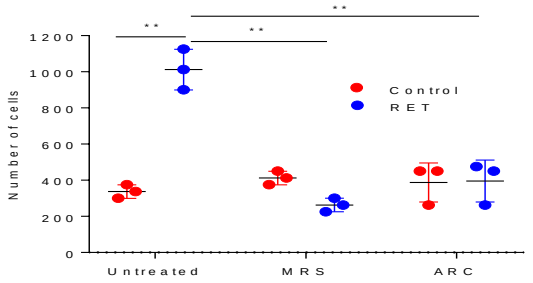
ATP hydrolysis



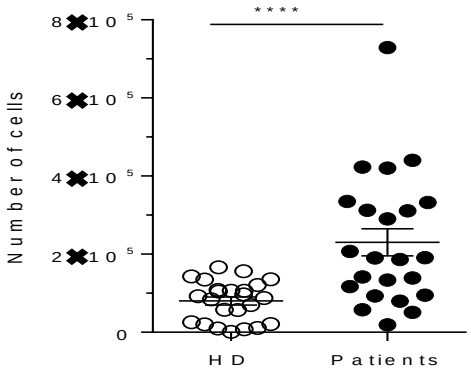
Inhibition of purinergic receptors

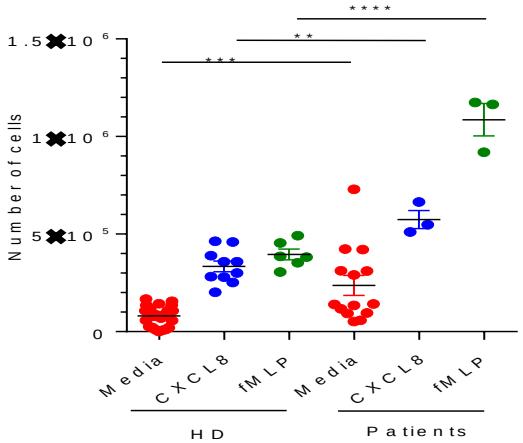


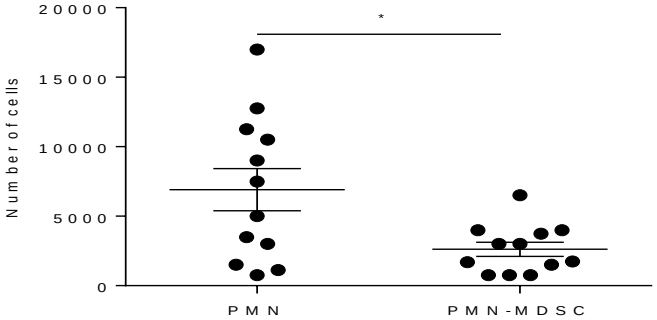


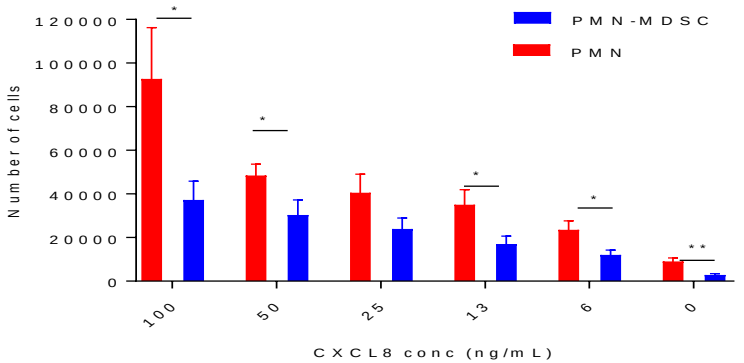


Migration of human neutrophils and PMN-MDSC

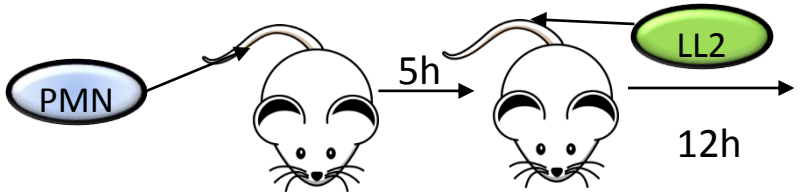




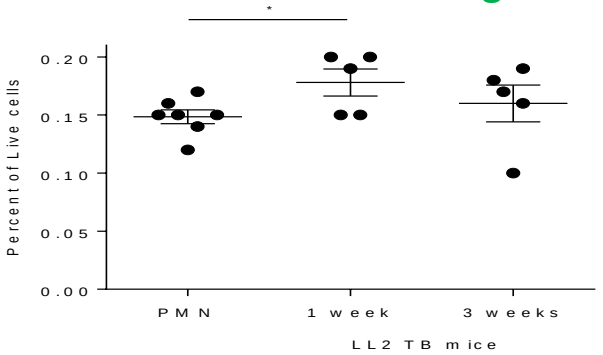


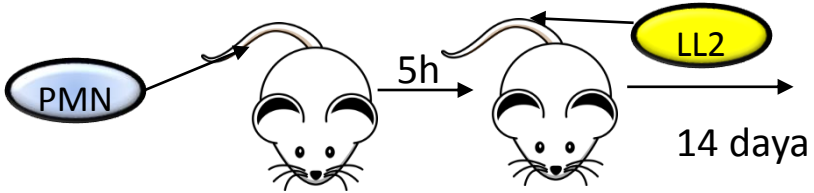


PMN-MDSC like cells promote metastasis better than PMN-MDSC

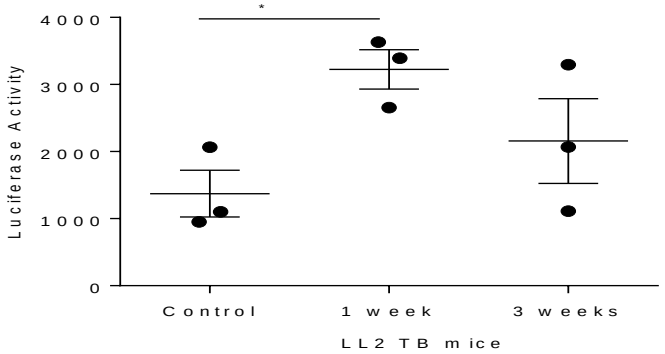


Tumor cells in lungs

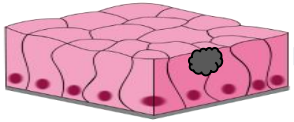




Tumor burden in lungs

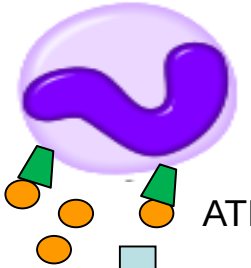


Early stage tumor, minimal inflammation

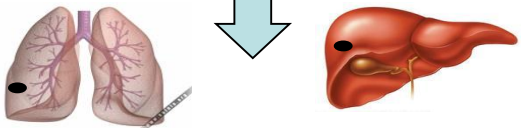


PMN-MDSC like cells

ER Stress, increased OXPHOS and glycolysis



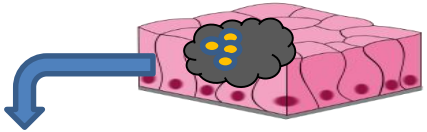
No suppression, potent spontaneous migration



Spontaneous migration to uninvolved tissues, promotion of tumor seeding and initial metastatic niche formation

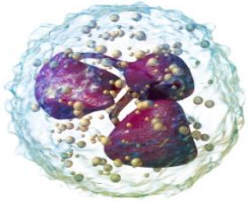
Bone marrow

Late stage tumors, strong inflammation

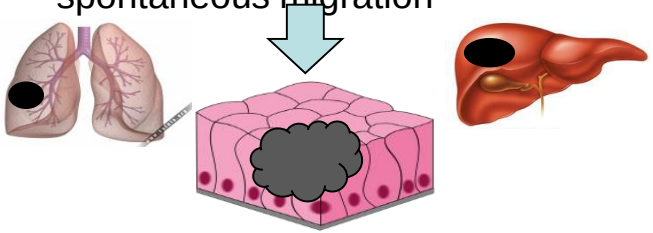


PMN-MDSC

ER stress, ROS, oxidative damage, NF-kB, inflammatory response



Immune suppression, minimal spontaneous migration



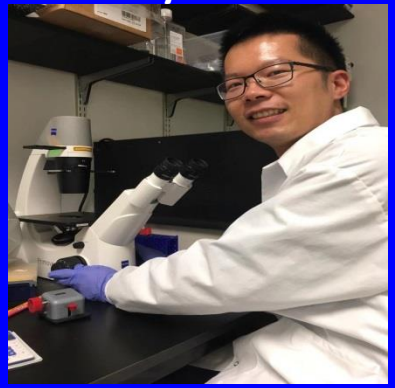
Promotion of tumor growth in primary and metastatic sites

Lessons and Take Home Messages

- MDSC are pathologically activated neutrophils and monocytes with preferential, but not exclusive feature of immature cells;
- MDSC are associated with poor clinical outcome in cancer;
- MDSC accumulate in advanced stage of cancer and are characterized strong immune suppressive activity;
- MDSC is extreme state of pathological activation of neutrophils. There are early stages of this process that are not associated with suppression but with increased metabolism and cell motility;
- At that stage neutrophils (provisionally termed MDSC like cells) actively migrate to uninvolved tissues and promote metastases.

Sima Patel

Shuyu Fu



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