Bone marrow adipocytes induce metabolic reprogramming of multiple myeloma cells

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Disclosure

Cristina Panaroni: No competing financial interests

Obesity, adiposity are positively correlated with myeloma progression

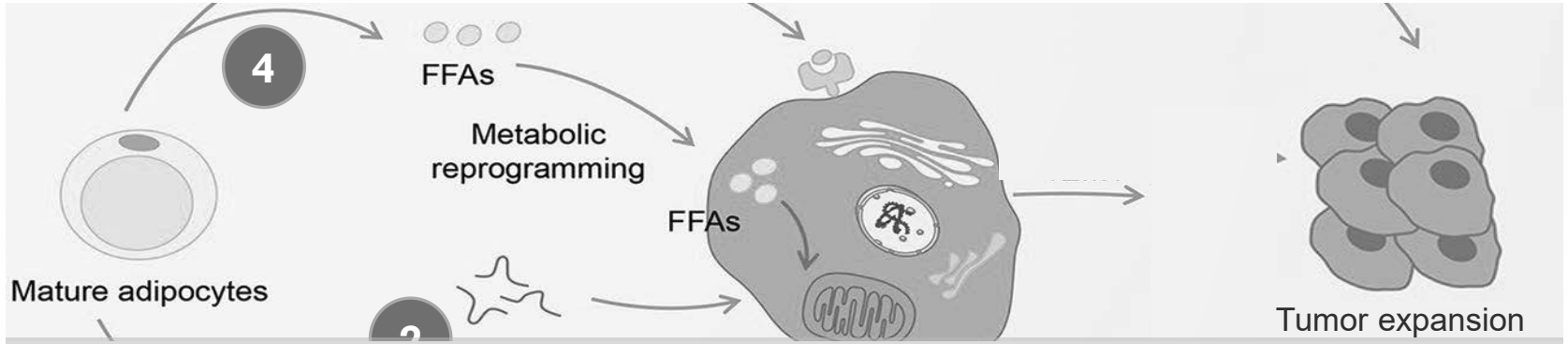
- Myeloma is highly dependent on bone marrow (BM) tumor microenvironment (TME) which changes with age and eventually comprises >70% of volume with BM adipocytes by the median MM patient's age of 65 years

- Obesity and lipid disorders, like Gaucher's, are associated with an increased risk of MM development *(Birmann et al., 2007; Landgren et al., 2010; Mistry et al., 2013; Chang et al., 2017)*

- Obesity-induced deregulation of lipids and diet-induced obesity were found to promote a myeloma-like syndrome in mice *(Lwin et al., 2015)*

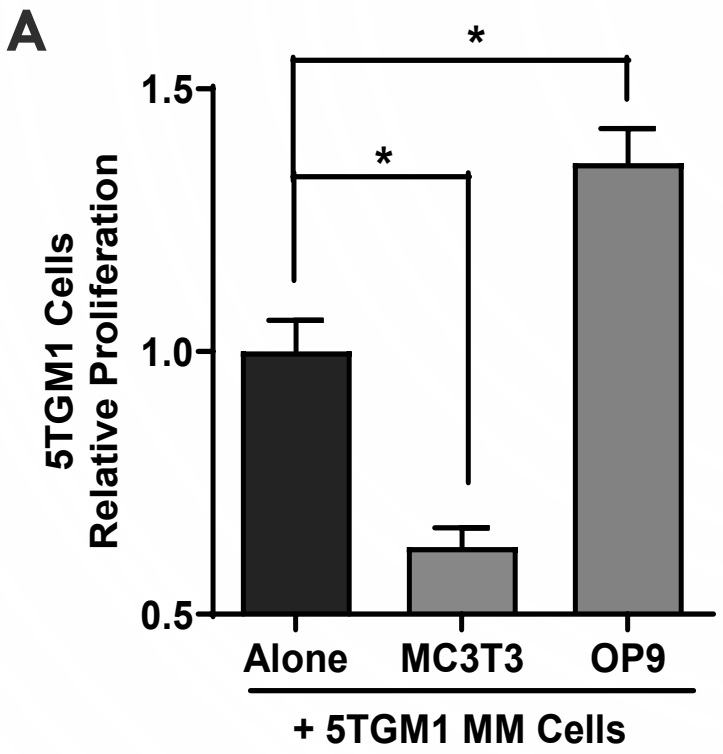
- Metabolomic and lipidomic profiling showed that complex fatty acids are decreased in the BM plasma samples from MM compared to MGUS patients *(Gonsalve et al., 2020)*

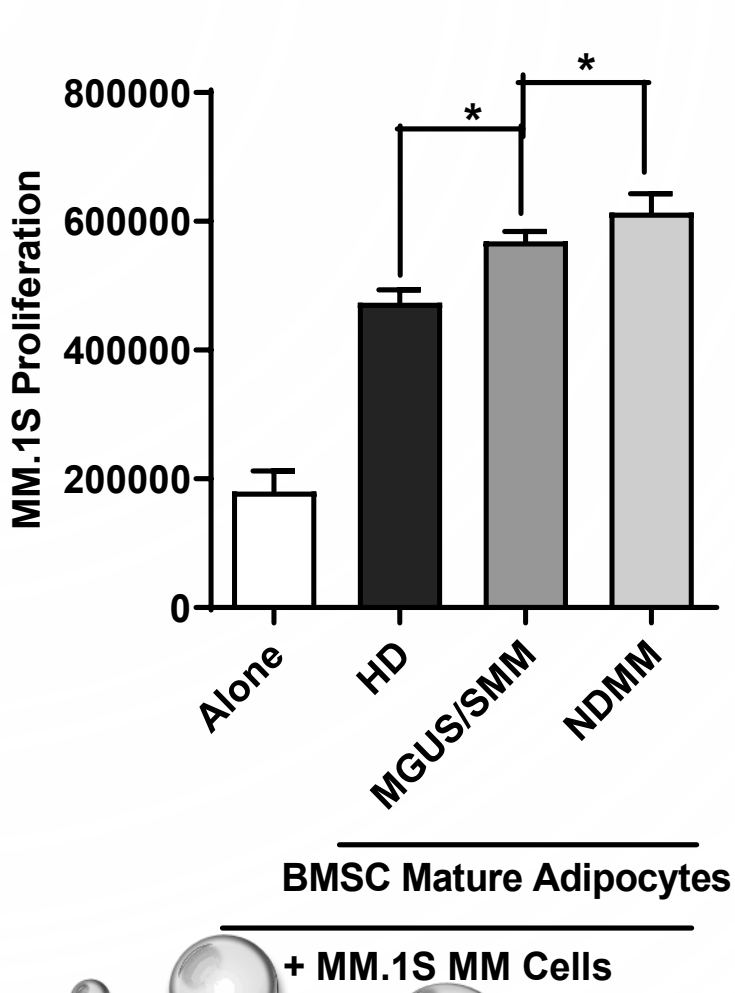
Cancer associated adipocytes support tumor cells through multiple mechanisms



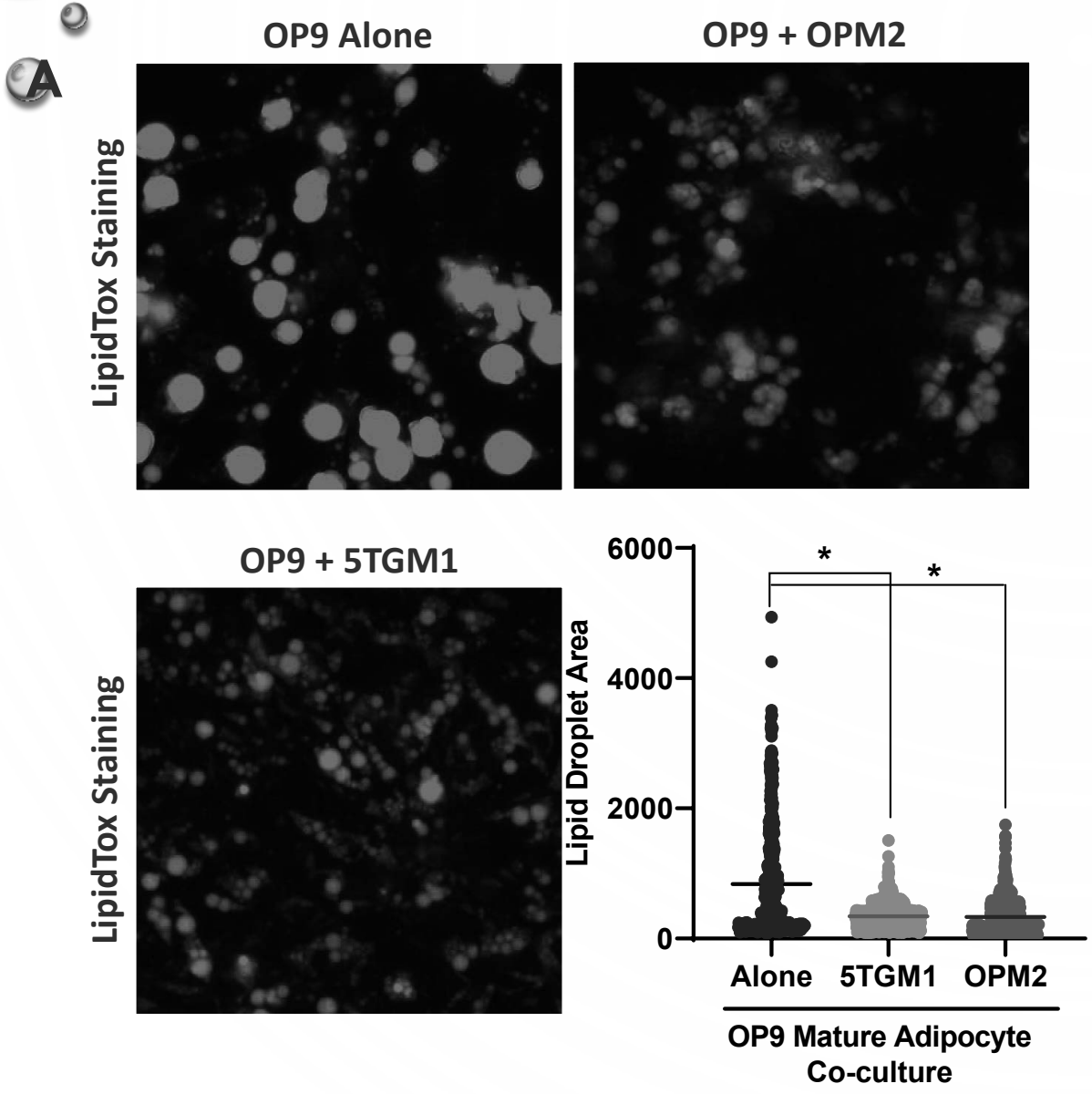
Bone marrow adipocytes support MM expansion by providing FFA for their metabolic reprogramming

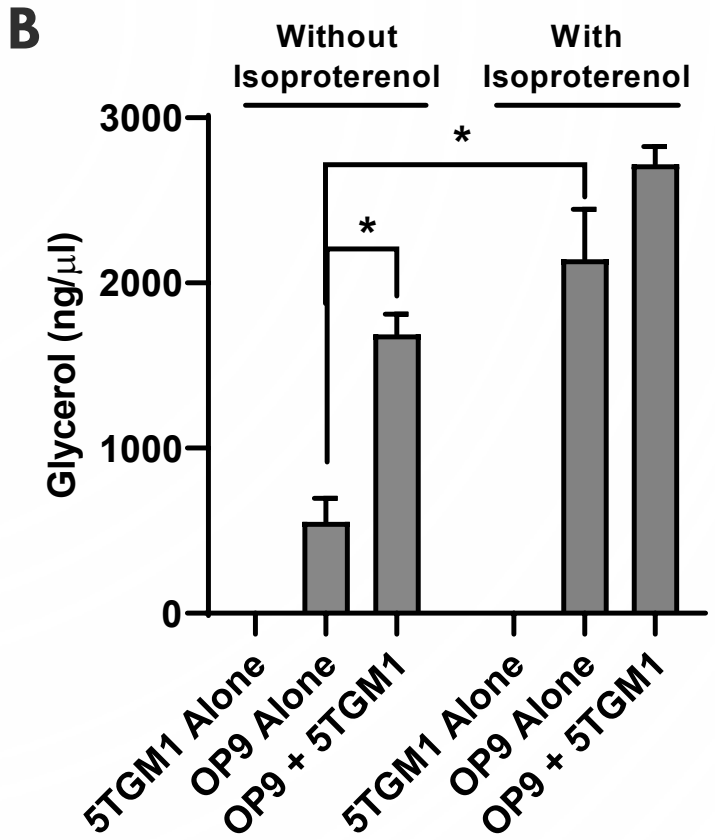
Adipocytes promote MM cell proliferation





MM cells induce lipolysis in adipocytes





FA metabolism genes are altered in mature BM adipocytes from MM patients

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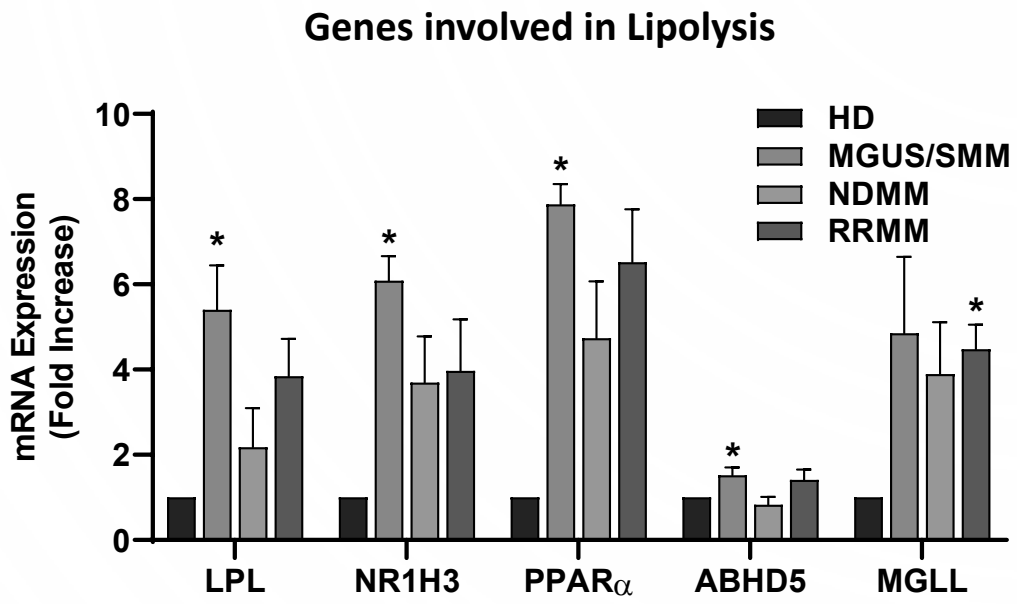

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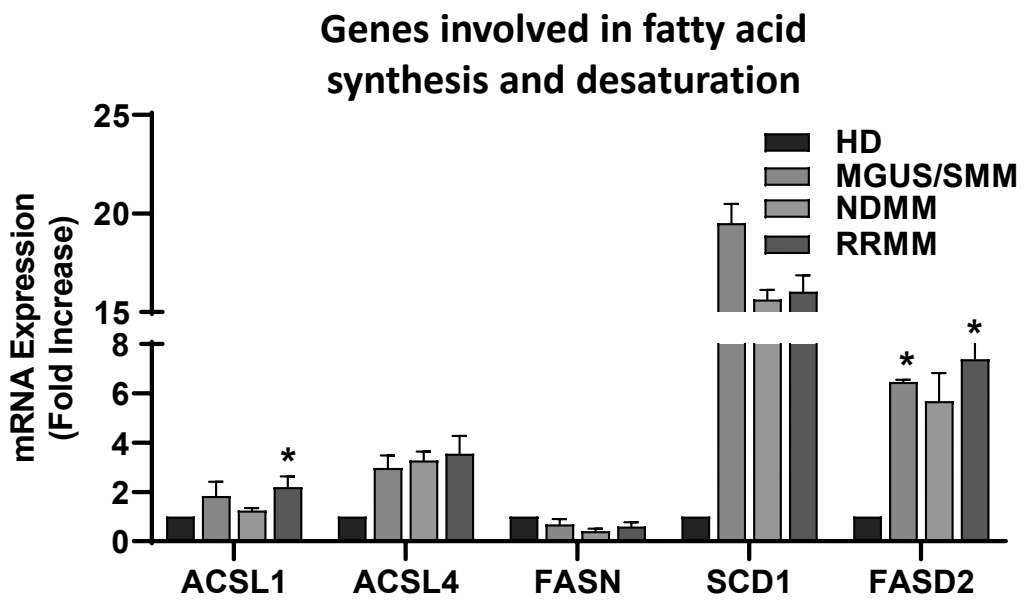
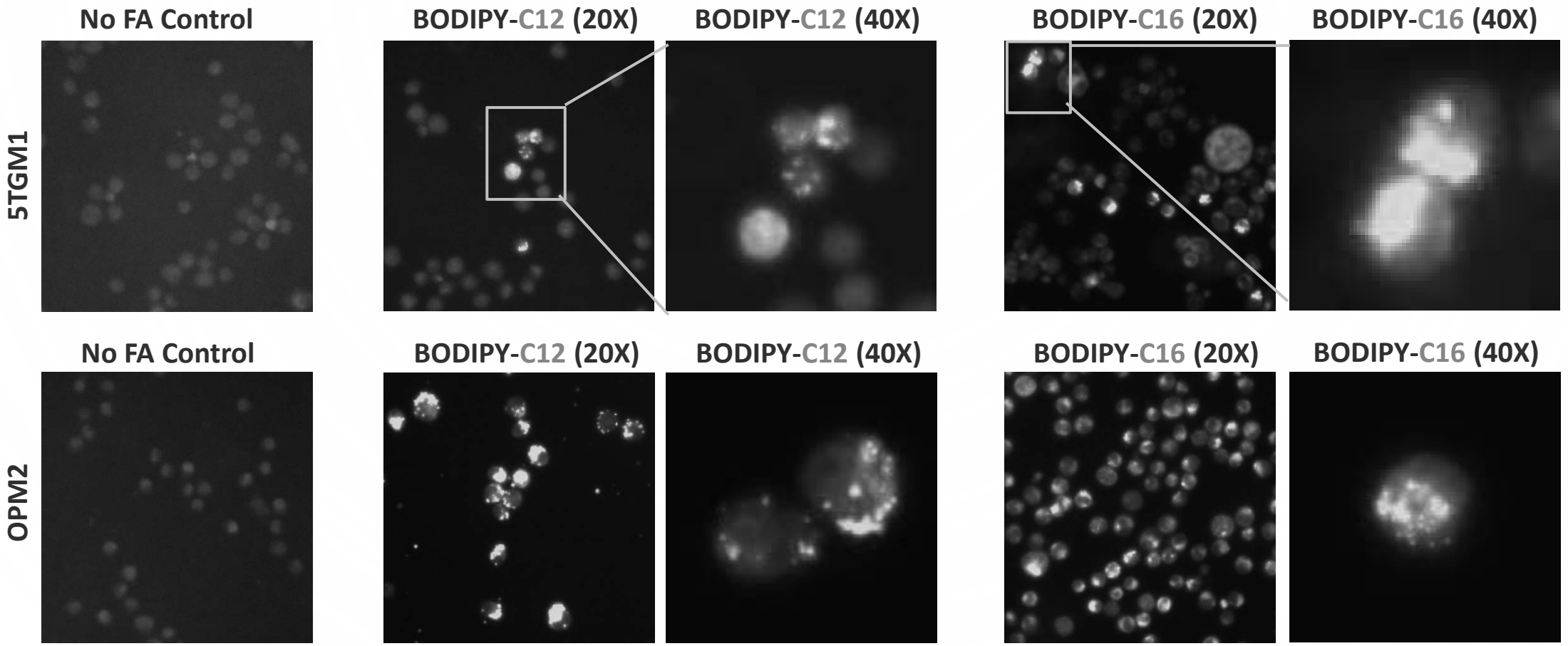


MM cells have cellular machinery to uptake FA



FA from adipocytes are directly transferred to MM cells

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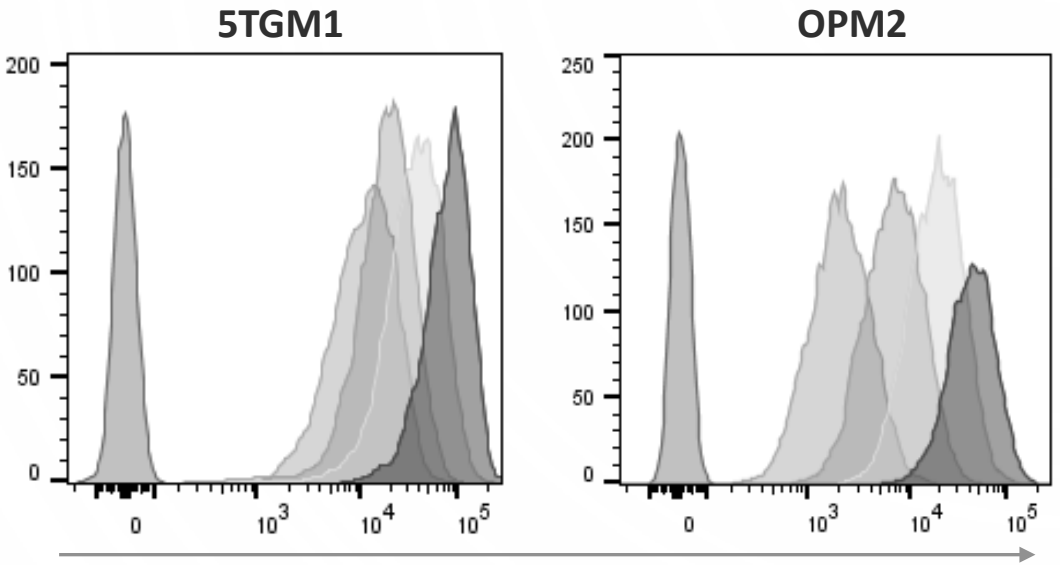

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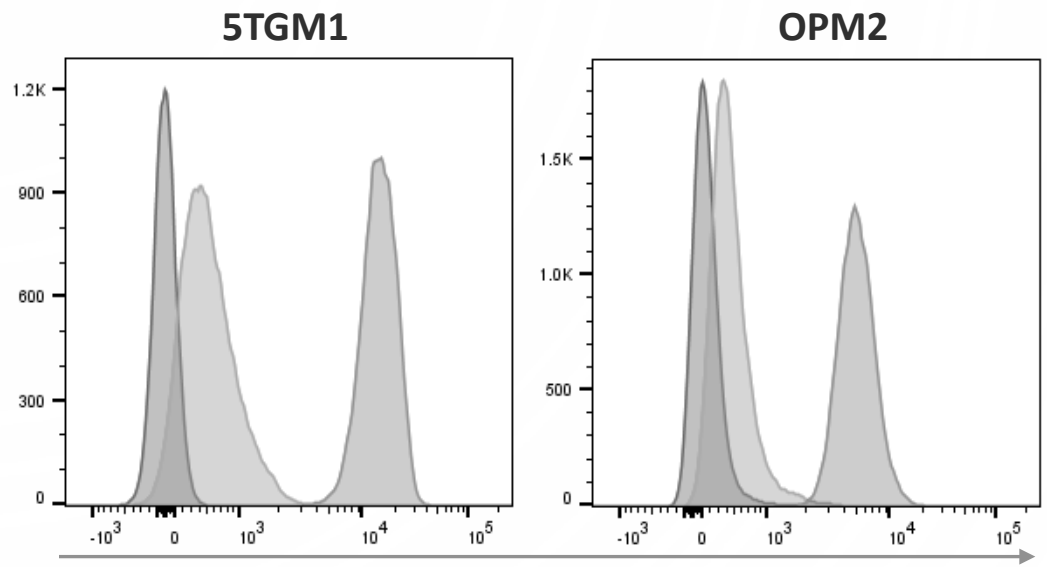
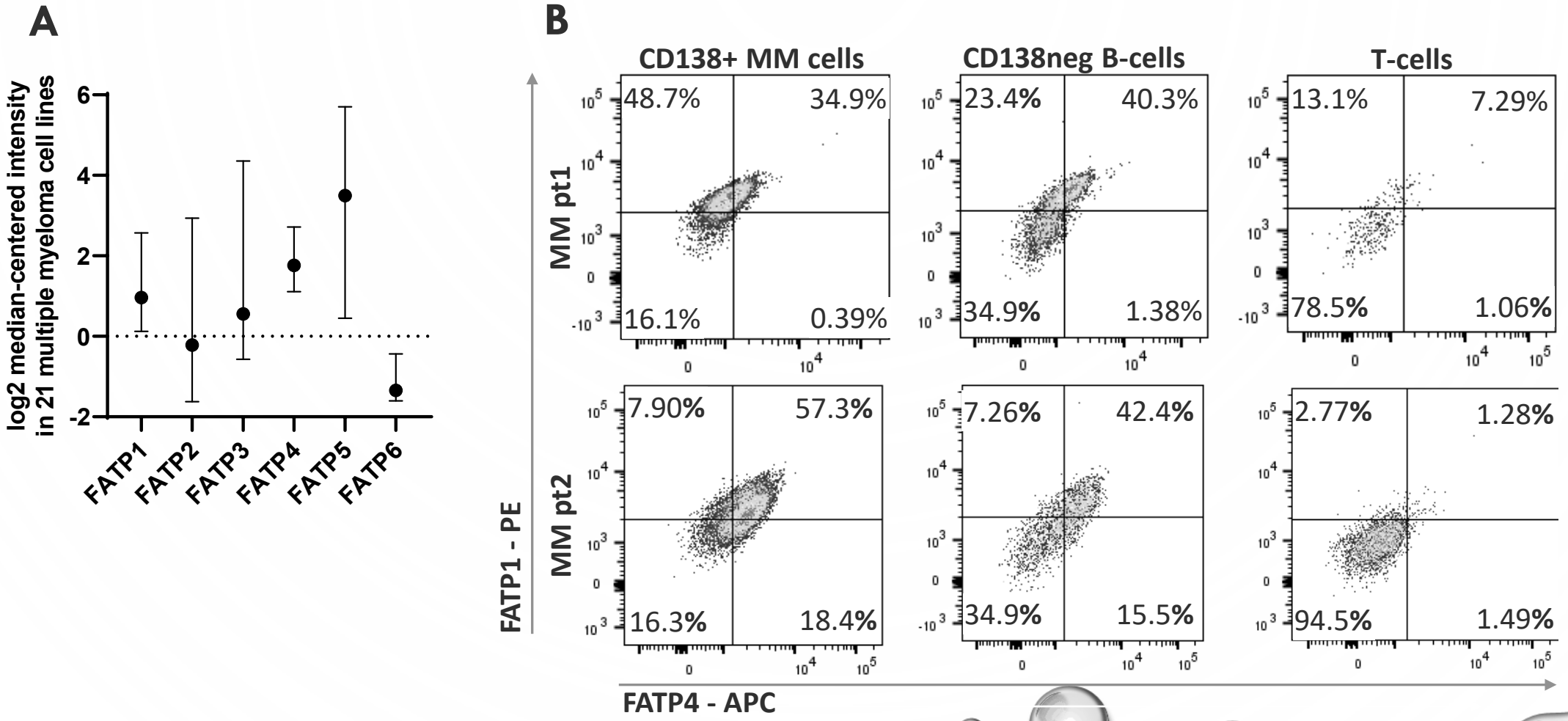


MM cells uptake FAs through Fatty Acid Transporter Proteins (FATPs)



Blocking lipolysis in adipocytes or FA-uptake through FATP in MM cells could be promising therapeutics strategies

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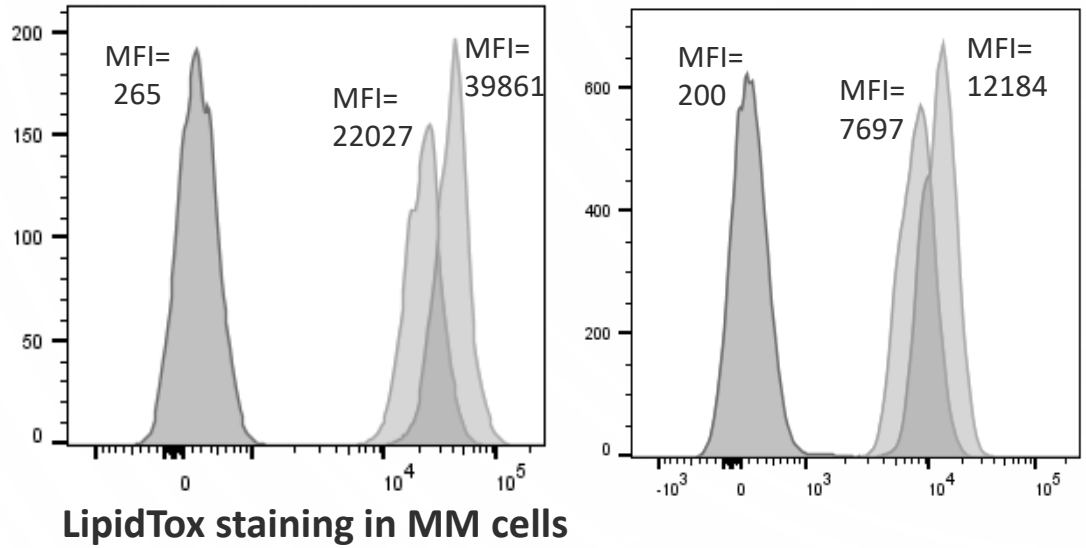
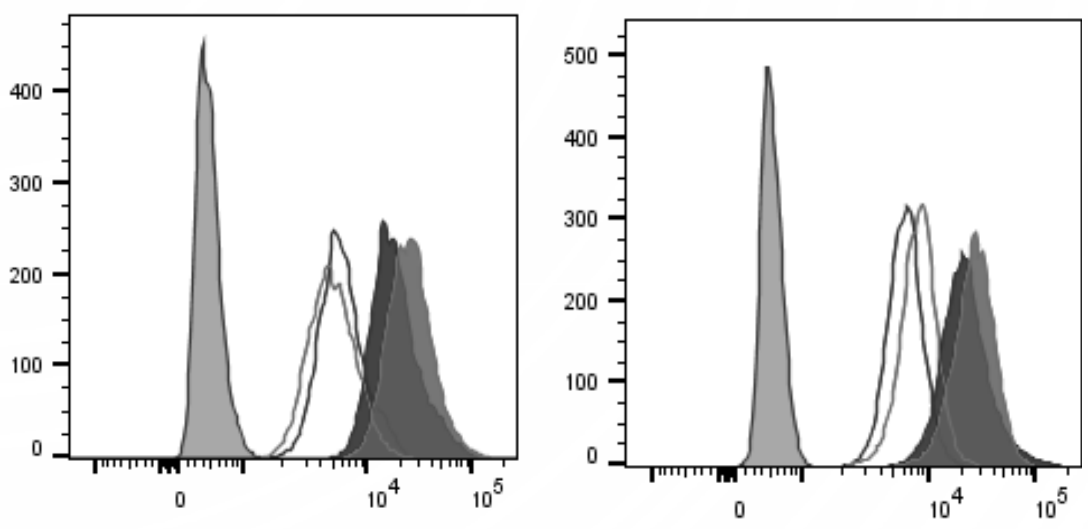


LipidTox staining in MM cells

- MM Cells Unstained
- MM Cells Co-cultured with OP9 Adipocytes Stained with LipidTox
- MM Cells Co-cultured with OP9 Adipocytes Stained with LipidTox and treated with **Acipomox**

B



- MM Unstained
- MM +Bodipy C12
- MM +Bodipy C16
- MM+Bodipy C12 + **Lipofermata**
- MM+Bodipy C16 + **Lipofermata**

Low-dose intake of Arachidonic Acid (AA) increases proliferation of MM cells whereas high-dose uptake decreases viability through ferroptosis-mediated lipotoxicity

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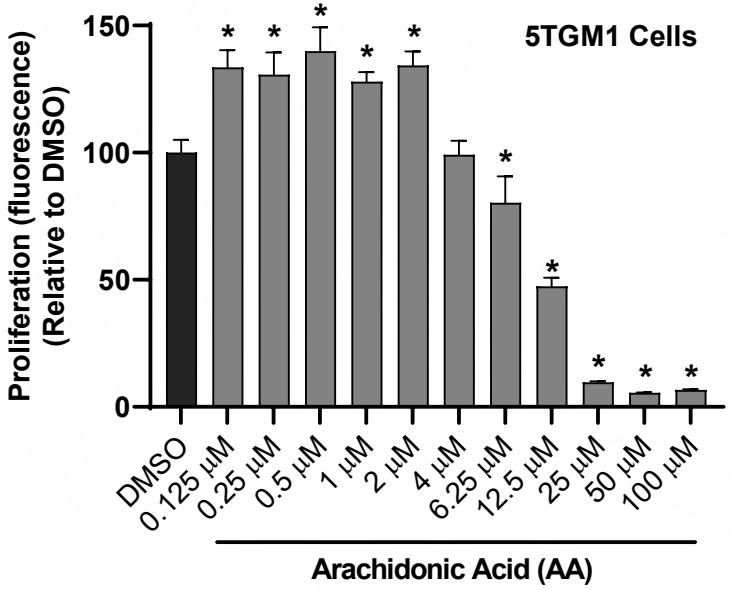

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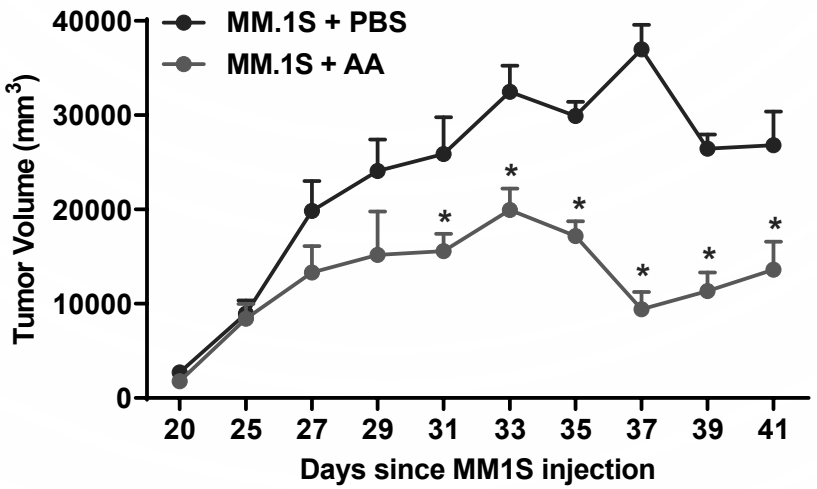

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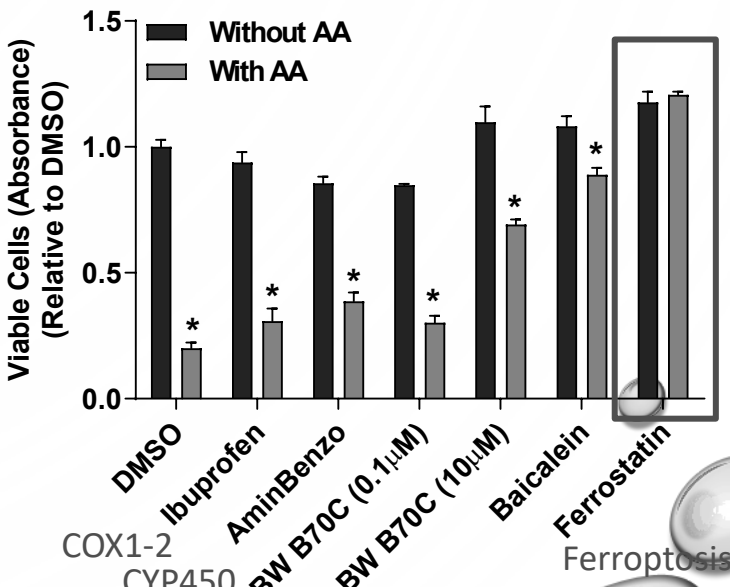
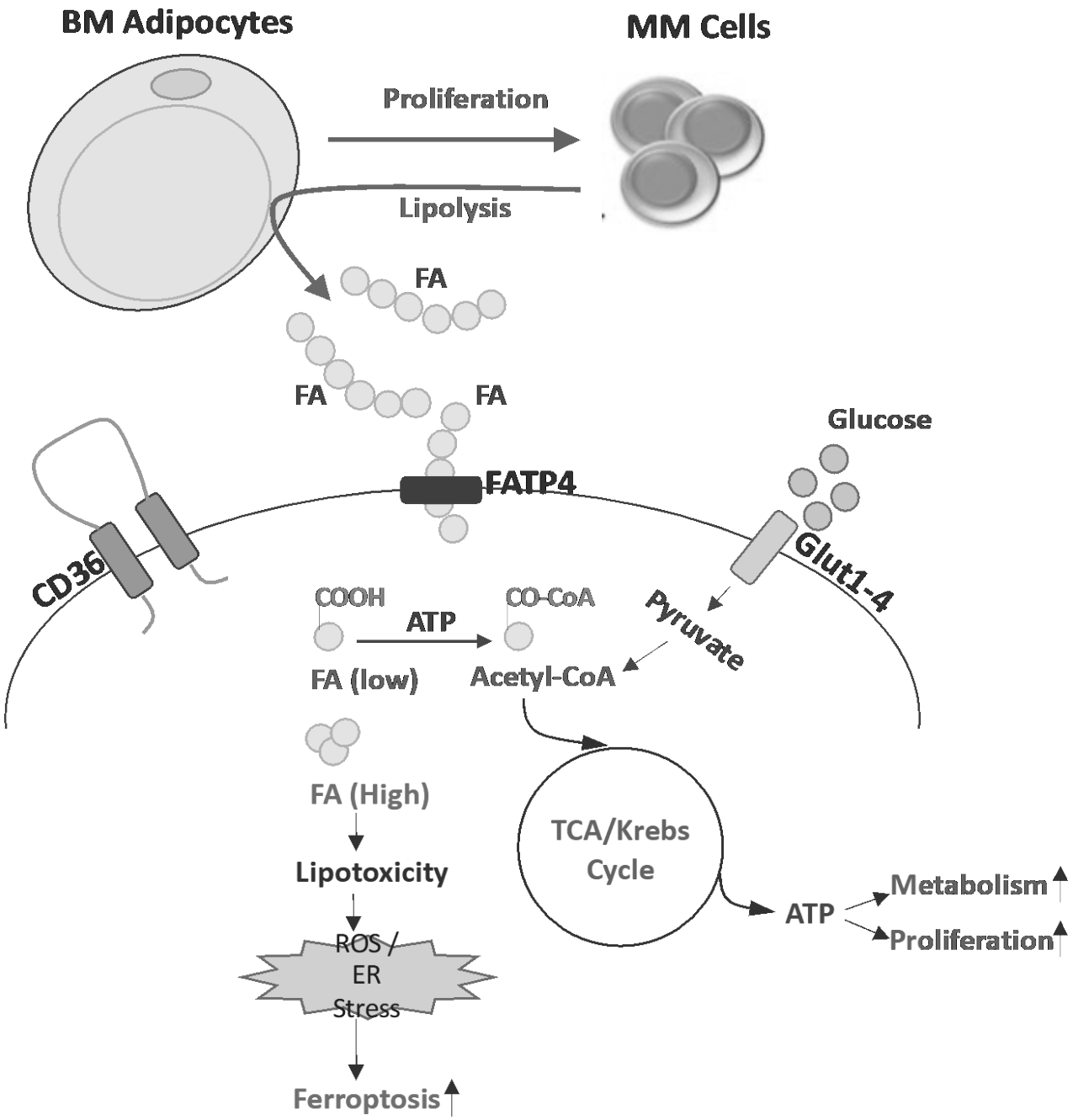


COX1-2
CYP450
Ferroptosis
5-15-12 LOX



Summary

- BMAds promote proliferation of MM cells
- MM cells induce lipolysis in co-cultured Ad
- FFA released through lipolysis are uptaken by MM cells through FATPs
- Low-dose intake of AA increase proliferation of MM cells whereas high-dose uptake reduces viability in-vitro and in-vivo through ferroptosis mediated lipotoxicity
- Inhibiting lipolysis in adipocytes or inhibiting uptake of FFA by MM cells through blocking of FATPs could be promising therapeutic strategy

Thank you for your attention!

MM cells rapidly uptake FA

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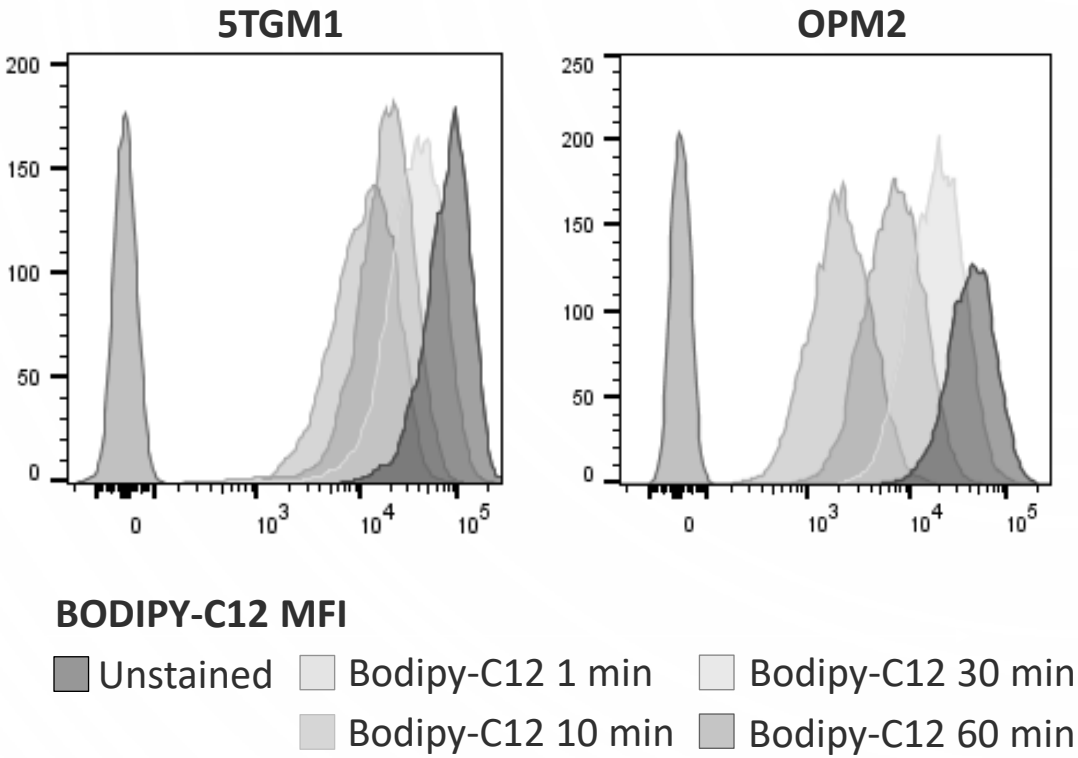

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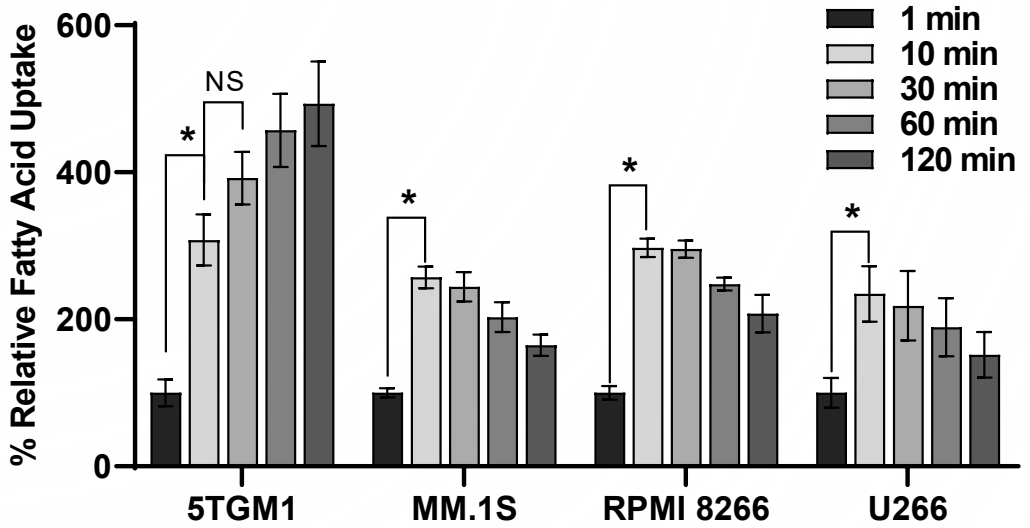
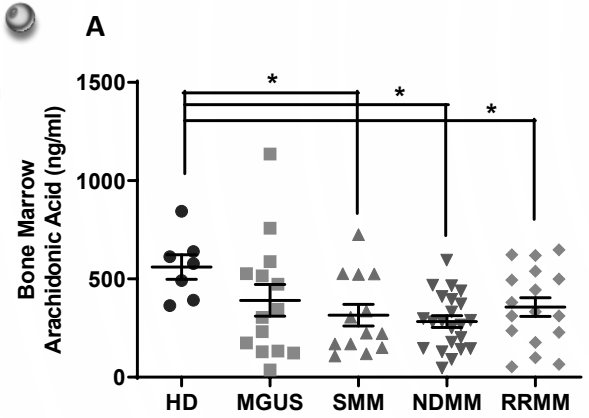
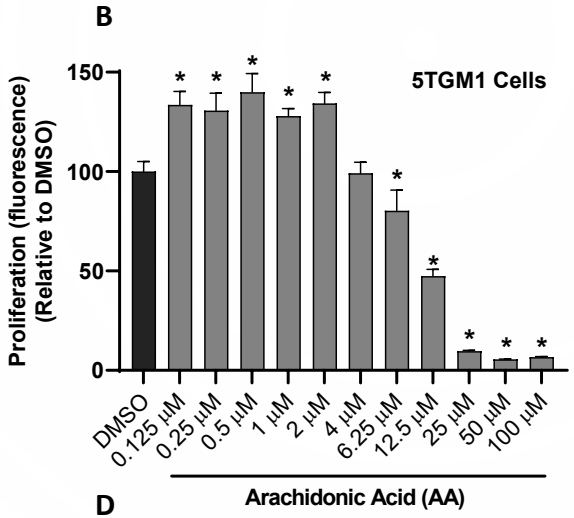
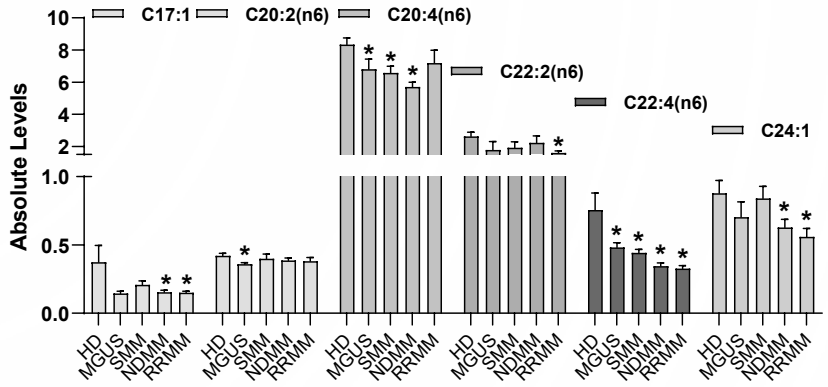
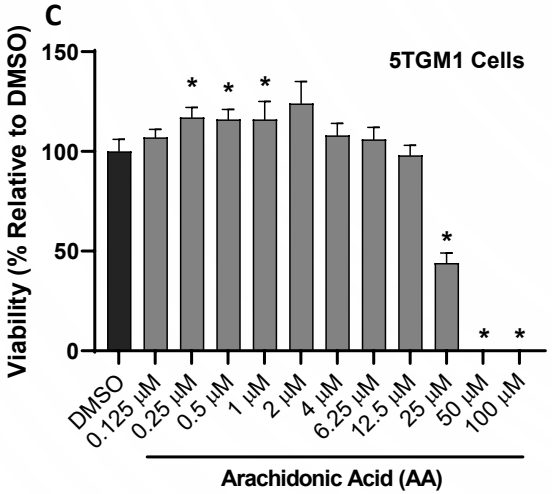


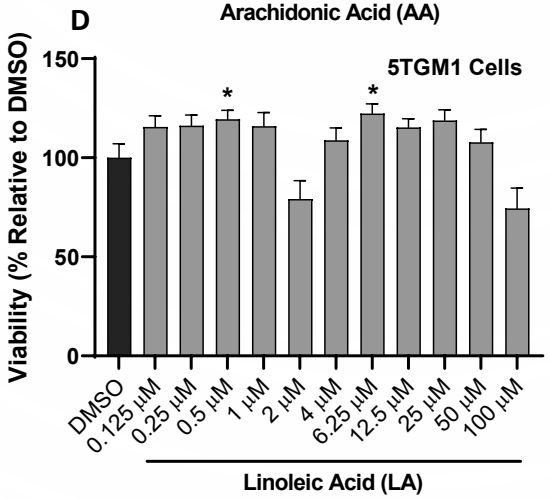
MM cells uptake Fatty acids through FATPs

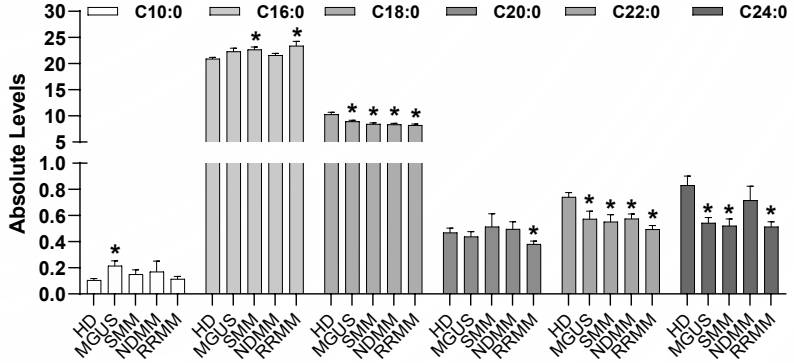












MM CELLS UPTAKE FATTY ACIDS THROUGH FATPS