Impact of Age and Fat Content on Toxicities Due to Pro-inflammatory Cytokine Storm Induced During Immunotherapy

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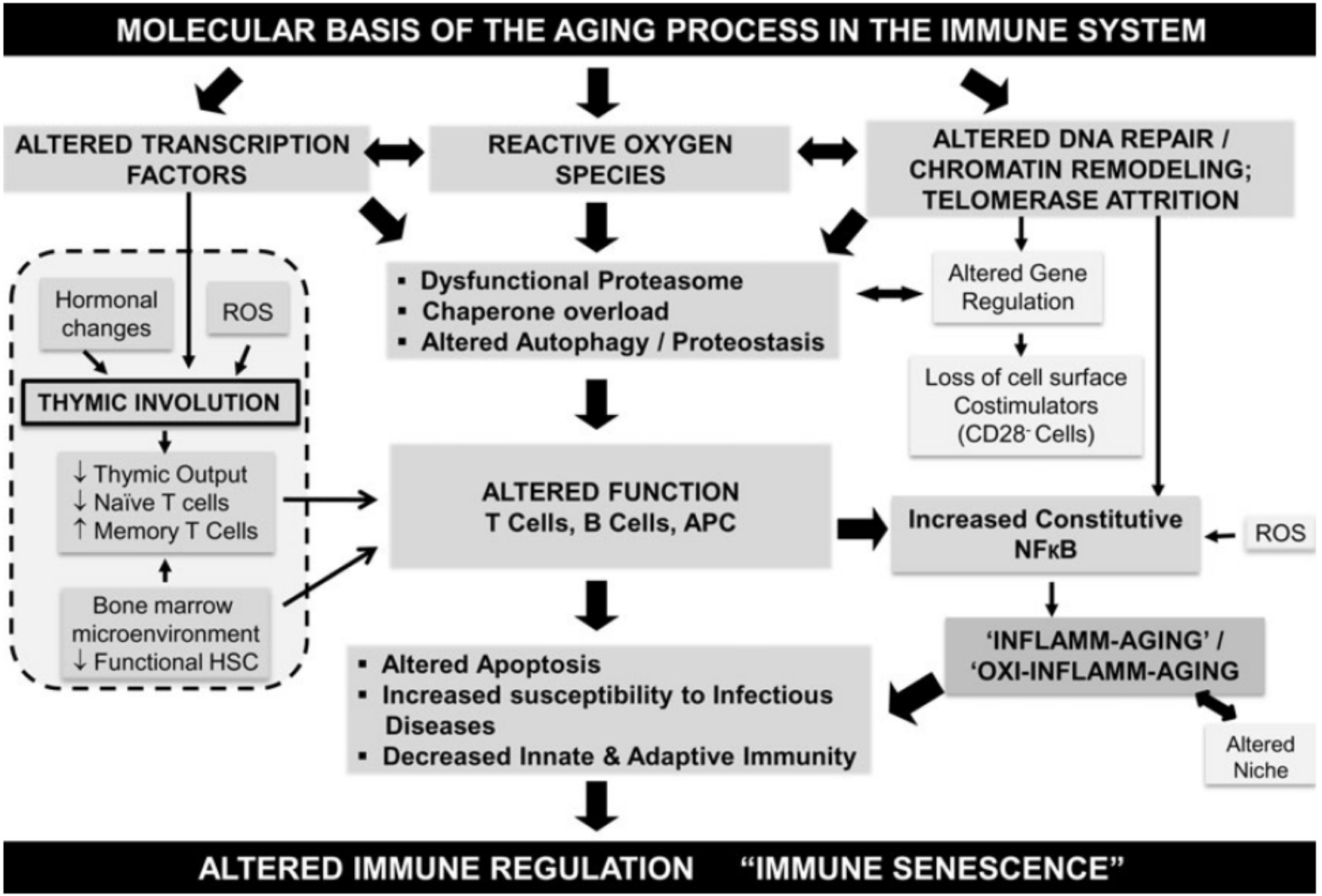
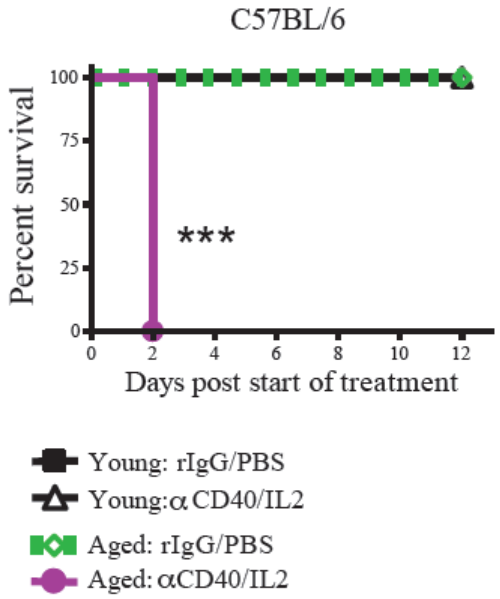
UCDAVIS

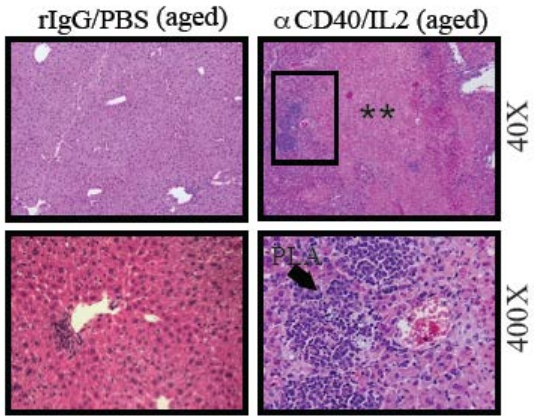


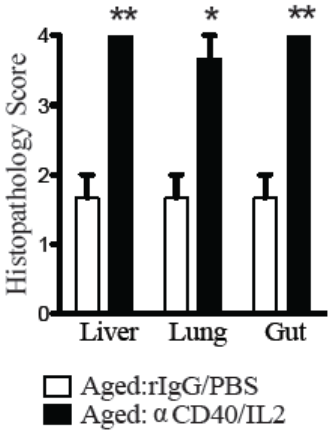
Ponnappan, S et al. Aging and Immune Function: Molecular Mechanisms to Interventions. 2011

GIVEN THE AVERAGE AGE OF A CANCER PATIENT, WHAT IS THE IMPACT OF AGE ON IMMUNOTHERAPY?

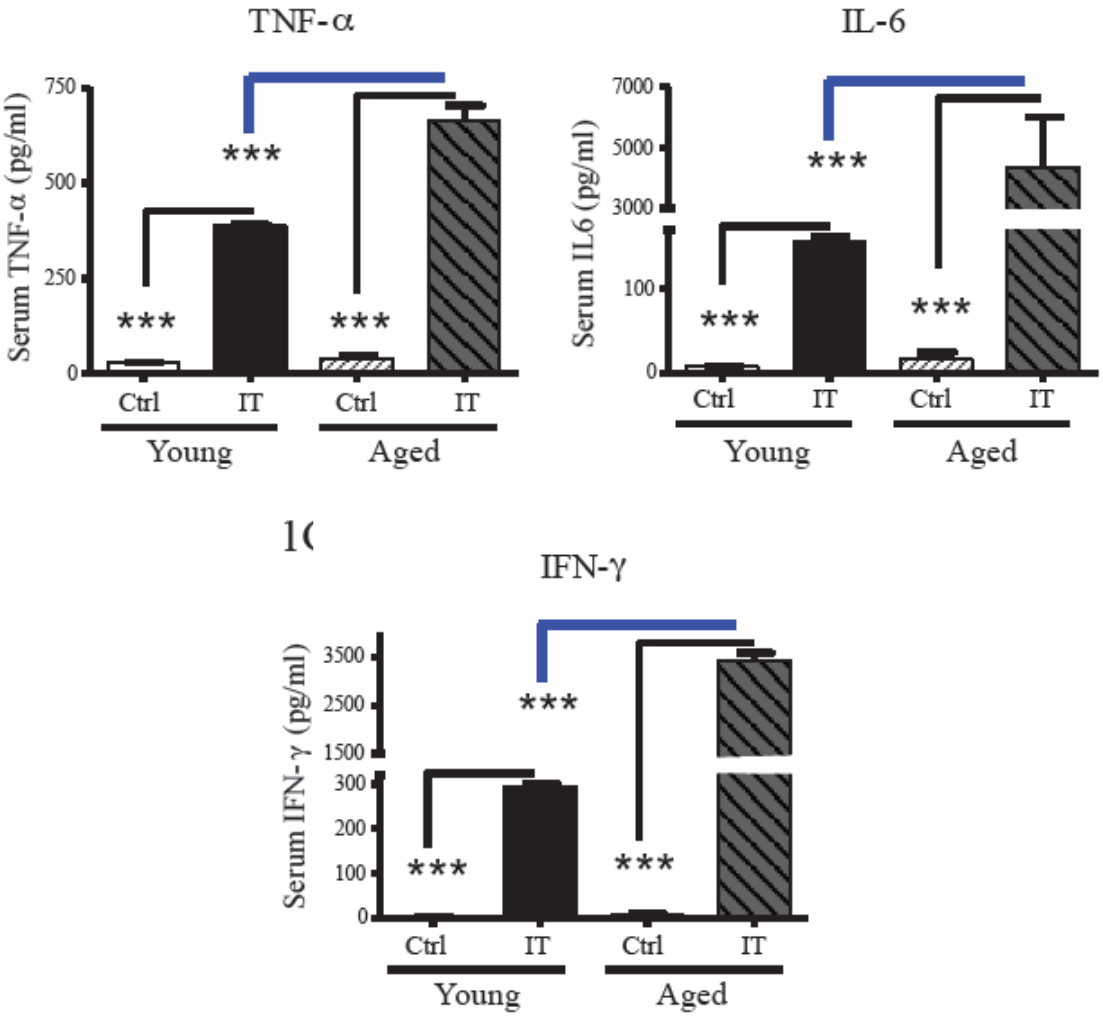
AGED MICE RAPIDLY SUCCUMB TO MULTI-ORGAN PATHOLOGY FOLLOWING IMMUNOTHERAPY



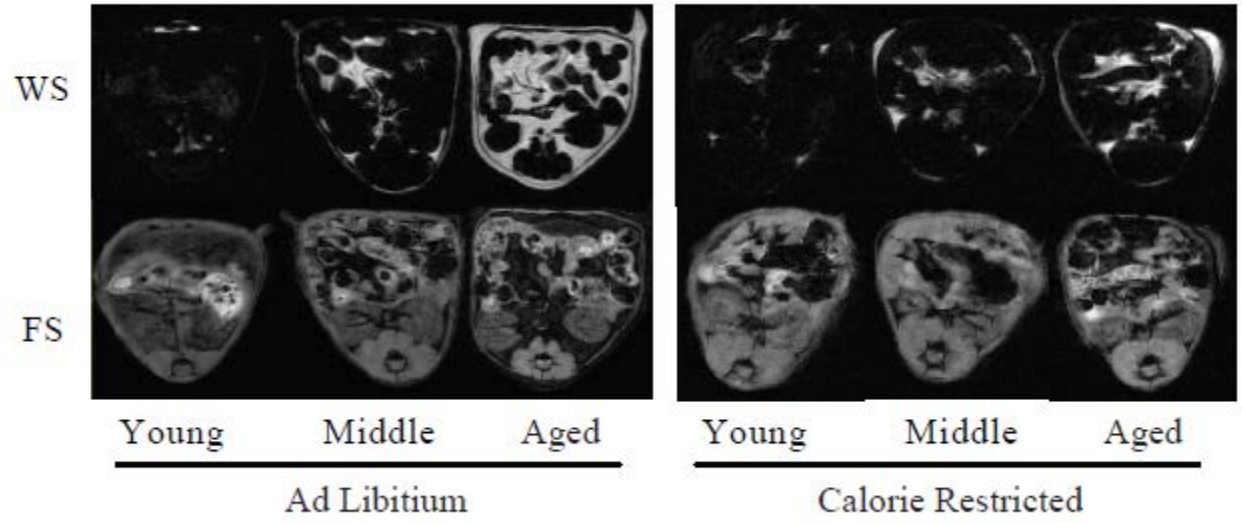


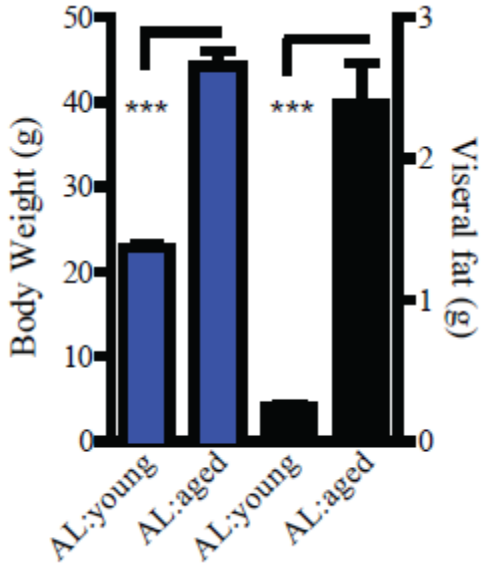


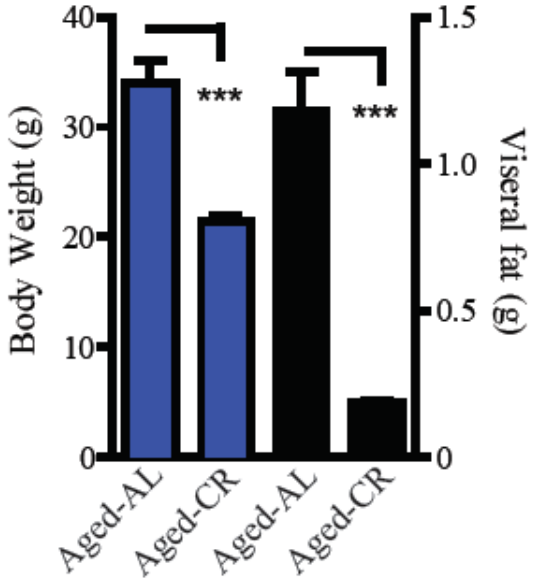
INCREASED PRO-INFLAMMATORY CYTOKINES FOLLOWING IMMUNOTHERAPY IN AGED MICE



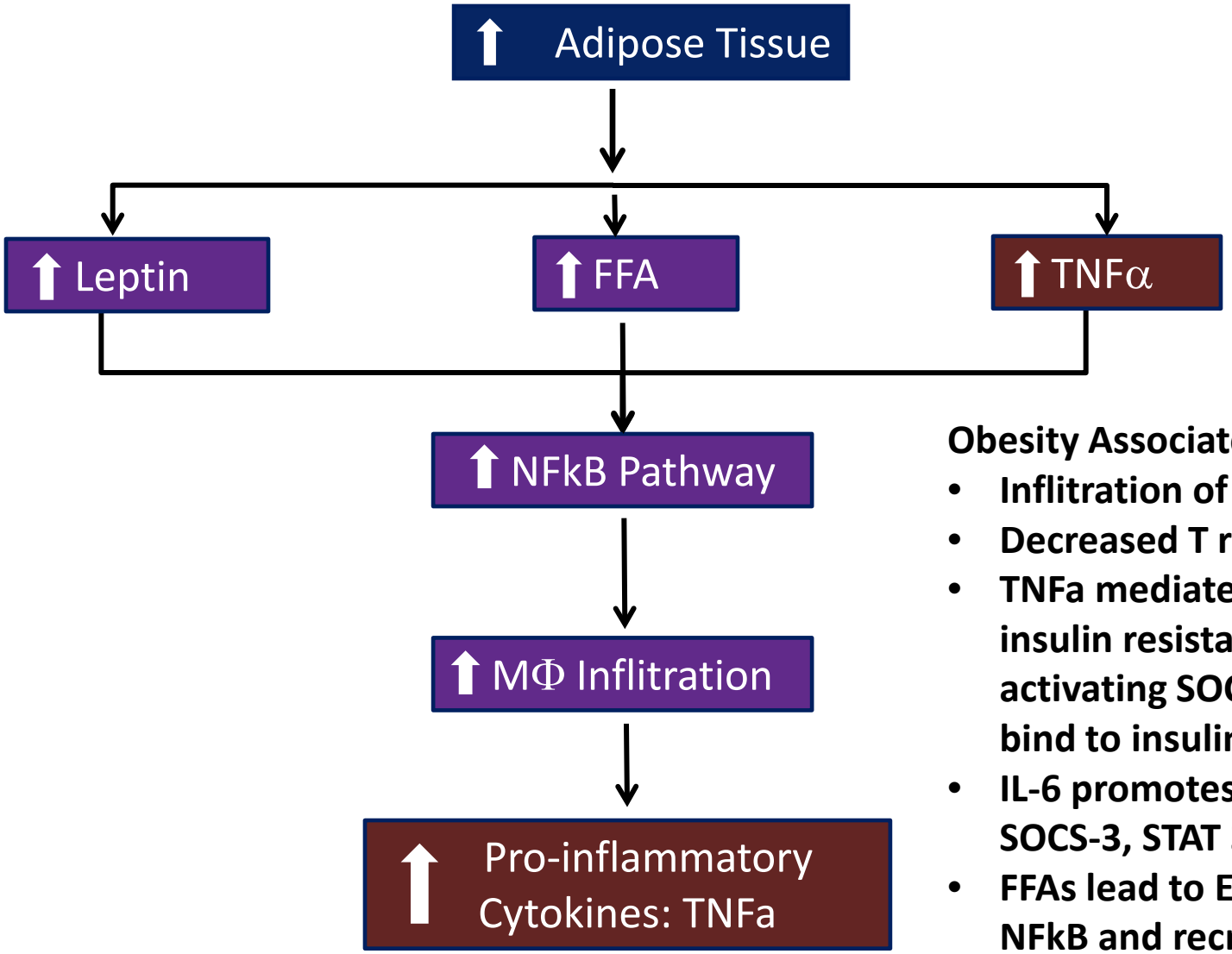
DIFFERENCES IN BODY FAT CONTENT WITH AGE AND CALORIC RESTRICTION







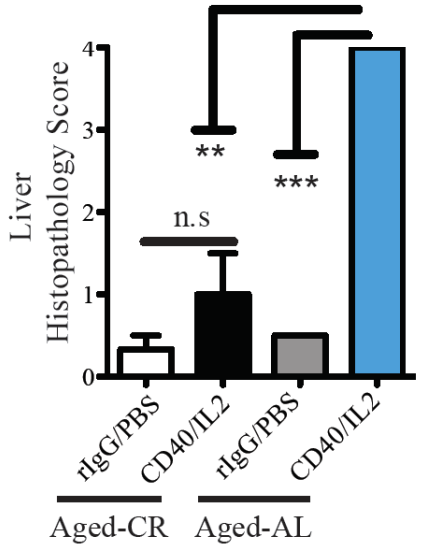
ROLE OF FAT IN INFLAMMATORY PROCESSES

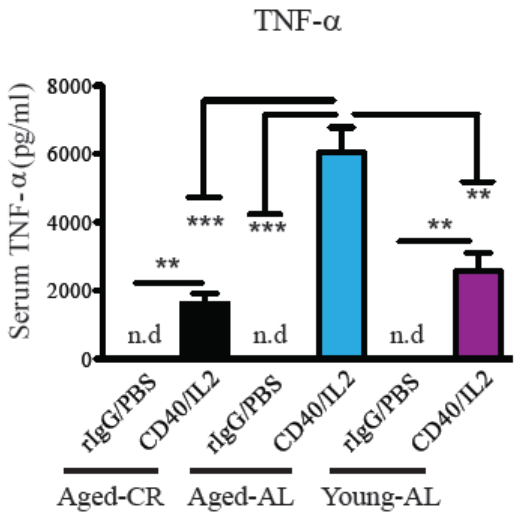


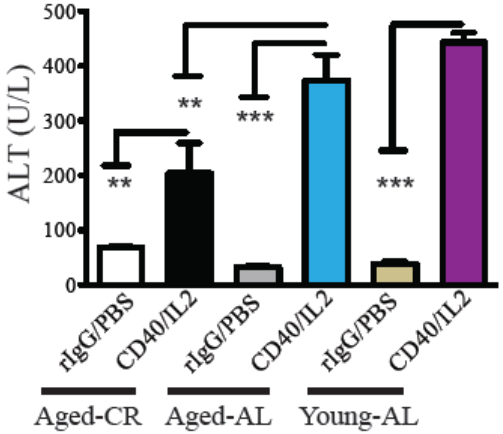
Obesity Associated With:

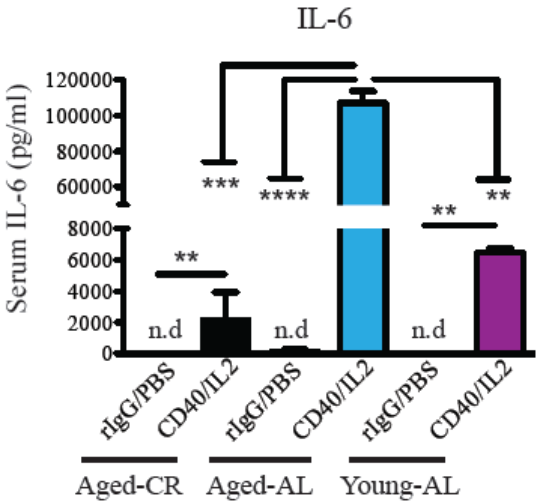
- **Inflitration of CD8s, MOs**
- **Decreased T regs**
- **TNFa mediated induction of insulin resistance (IR) by activating SOCS proteins that bind to insulin receptor**
- **IL-6 promotes IR by activating SOCS-3, STAT 3-5**
- **FFAs lead to ER stress activating NFkB and recruitment of immune cells**

CALORIC RESTRICTION RESCUES AGED MICE FROM EXACERBATED CYTOKINE STORM AND ACUTE TOXICITY

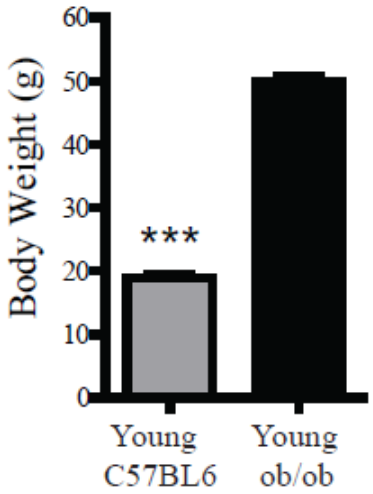


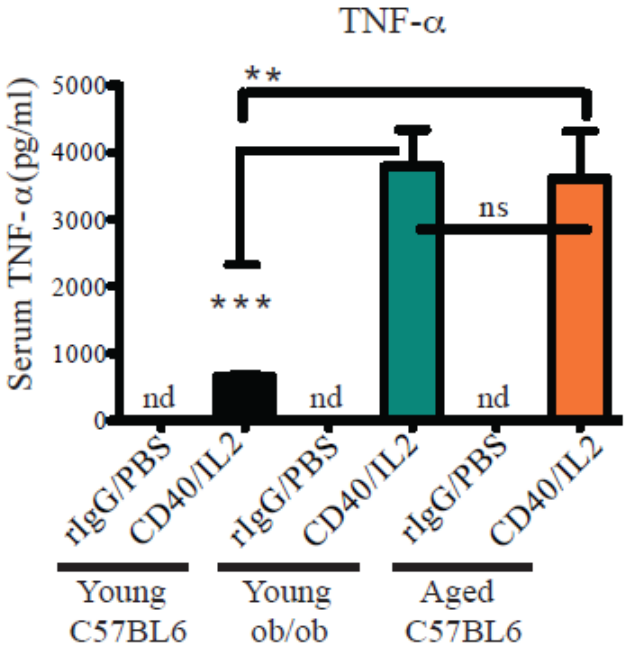




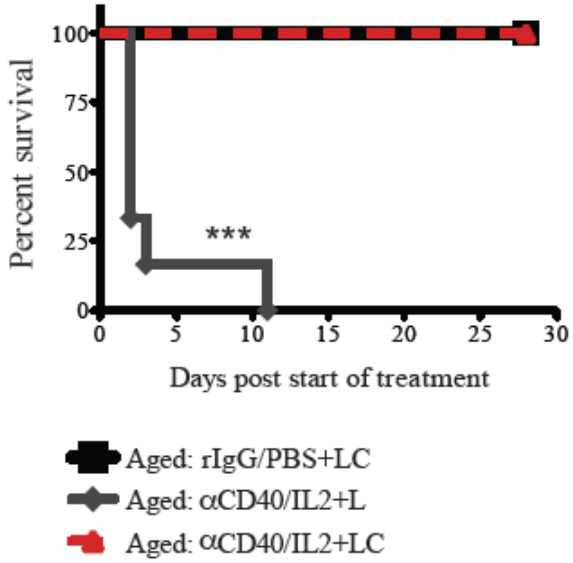


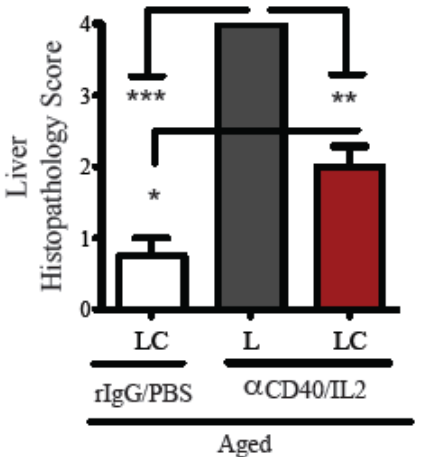
YOUNG OBESE MICE EXPRESS HEIGHTENED LEVELS OF PROINFLAMMATORY CYTOKINES SIMILAR TO AGED

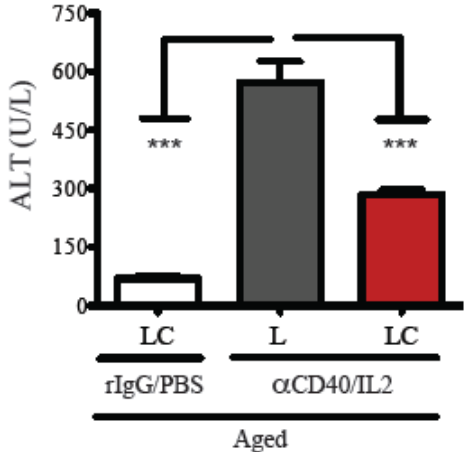


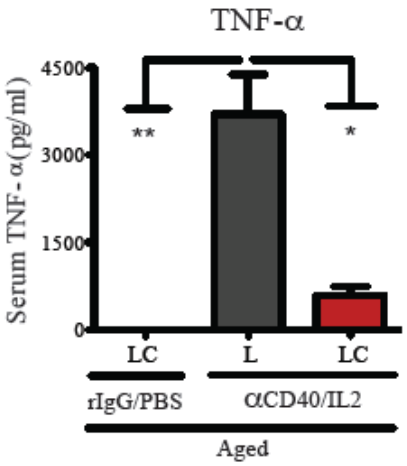


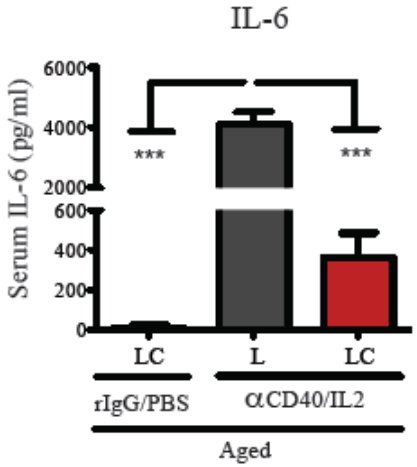
MACROPHAGE DEPLETION PROTECTS AGED MICE FROM ACUTE TOXICITY AND DIMINISHES CYTOKINE STORM



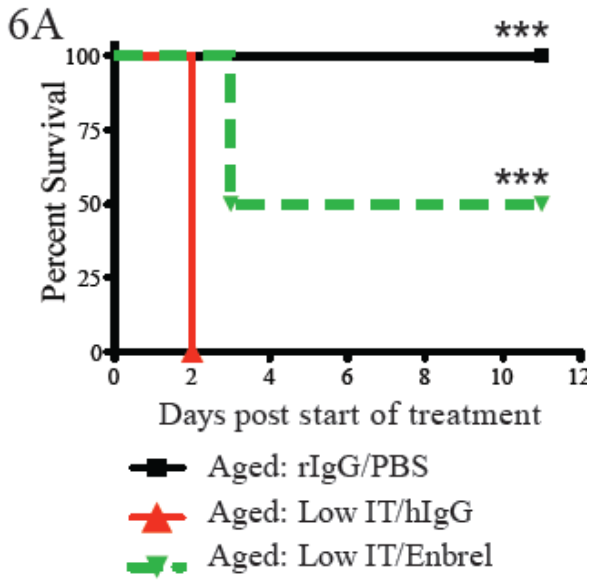


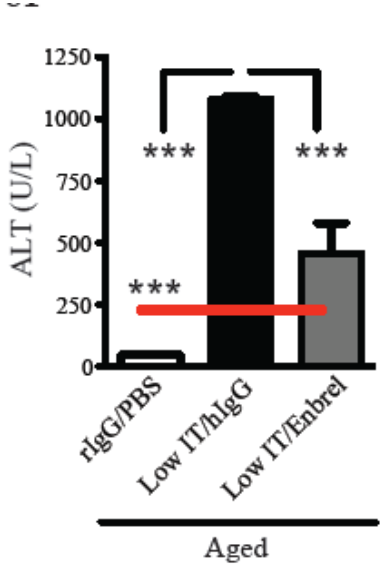




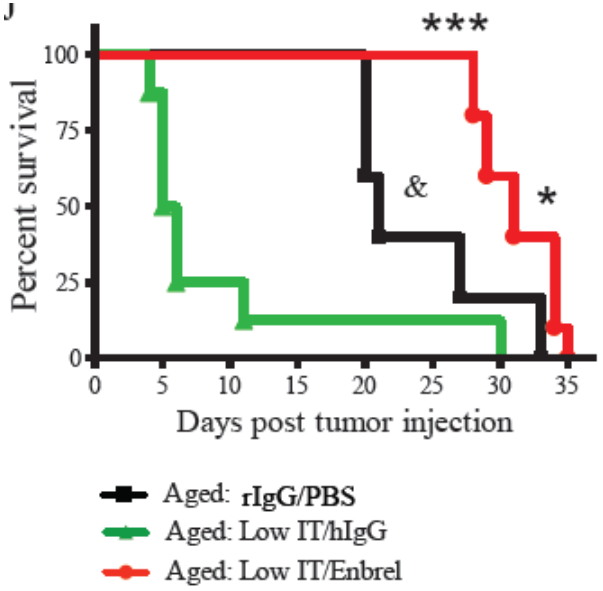


TNF-BLOCKADE RESCUES AGED MICE FROM ACUTE TOXICITY FOLLOWING IMMUNOTHERAPY





CONCURRENT TNF-BLOCKADE WITH IMMUNOTHERAPY ALLOWS FOR ANTITUMOR EFFECTS IN AGED MICE



CONCLUSIONS

- FOLLOWING IT, AGED MICE EXHIBIT:
  - CYTOKINE STORM: ELEVATED TNFa, IL-6, and IFNg
  - MULTIORGAN FAILURE, RAPID DEATH
  - MACROPHAGE DEPENDENT
  - TNFa CRUCIAL MEDIATOR

- BODY FAT PLAYS ROLE IN EXACERBATED CYTOKINE PRODUCTION

- AGE and BODY FAT MAY PLAY SIGNIFICANT ROLES IN CLINICAL CANCER THERAPY OUTCOMES

ACKNOWLEDGEMENTS

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