

## INTRODUCTION

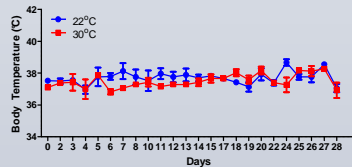
- Many cancer research laboratories utilize mouse models to study tumor responses to therapies *in vivo*. These studies are essential for studying the effectiveness of the therapies before they are allowed to moved to clinical trials.
- Under standard housing conditions laboratory mice experience various metabolic stresses, including chronic cold stress.
- Standard housing conditions are 22°C even though the thermoneutral temperature of mice is 30°C. As a result, the mice need to expend a great deal of energy to maintain their normal core temperature of 37°C.
- By altering the metabolism of the host, essentially through metabolic stresses, changes may be occurring in the tumor biology or tumor microenvironment that are compromising the accuracy of the models and leading us to question the efficacy of the therapies being studied.

## QUESTION

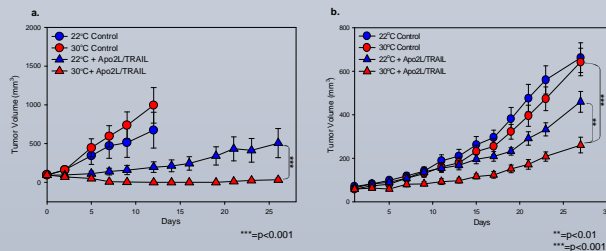
- Does this chronic cold stress, caused by housing mice at sub-thermoneutral temperatures, support pro-survival mechanisms in the tumors and cause resistance to these therapies?

## BACKGROUND

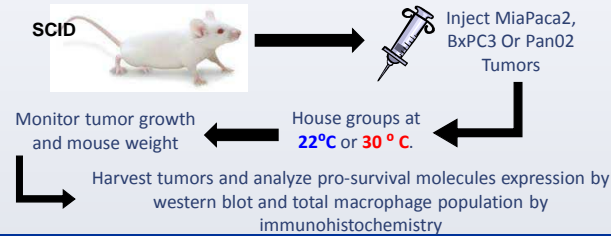
- At standard and thermoneutral conditions mice maintain their core body temperature of 37°C.
- Therefore, mice housed at standard conditions, 22°C must increase their metabolic rate to maintain constant body temperature.



- In preliminary experiments, sensitivity to Apo2L/TRAIL, a cancer therapy that targets the apoptosis pathway, increases in mice housed at their thermoneutral temperature of 30°C.
- This increased sensitivity was observed in xenograft models with human pancreatic cancer cell lines, (a) MiaPaca2 and (b) BxPC3.



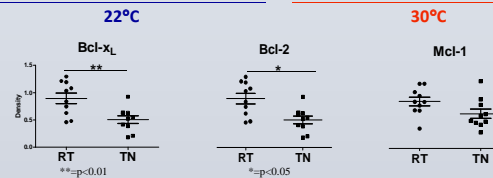
## EXPERIMENTAL DESIGN



## RESULTS

Expression of pro-survival molecules at 22°C and at 30°C.

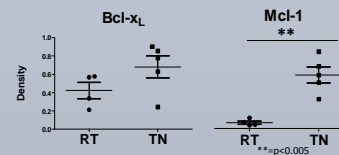
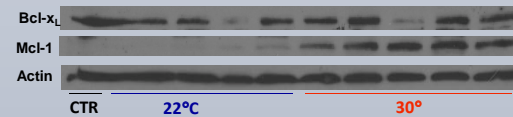
### MiaPaca2 Xenograft Tumors



### BXPC3 Xenograft Tumors

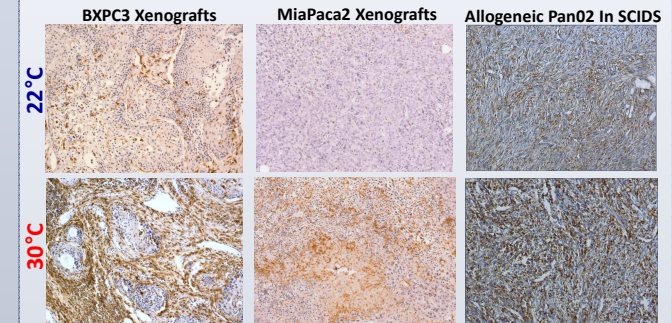


### Pan02 Allogeneic Tumors

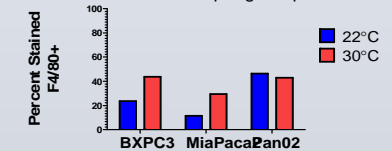


## RESULTS

Macrophage infiltration of the tumor microenvironment increases at 30°C in BXPC3 and MiaPaca2 Xenografts but not in Pan02 tumors.



IHC Stained Macrophage Population



## CONCLUSIONS

- Preliminary studies show that some tumors do respond differently to the same therapy when mice are housed at thermoneutrality.
- Housing mice at thermoneutrality increases sensitivity of MiaPaca2 and BxPc3 xenografts to Apo2L/TRAIL.
- MiaPaca2 tumors from untreated animals housed at thermoneutrality have significantly reduced levels of Bcl-x<sub>L</sub>, Bcl-2, and slightly reduced levels of Mcl-1.
- BXPC3 and MiaPaca tumor microenvironments show increased numbers of macrophages when stained by the macrophage marker F4/80.

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