Evaluating variation in preclinical colorectal oncology studies using mouse models to improve translational medicine

Rohit Satish, Dr. David Threadgill

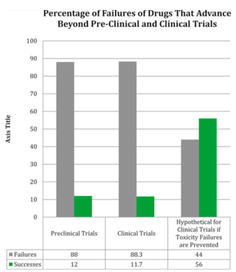
ABSTRACT

Mouse models are essential in preclinical colorectal cancer research to test drug and gene therapies. However, their results often don't translate well to humans, mainly due to confounding variables that affect the trials and lead to low reproducibility. By analyzing the genetic and environmental factors causing variability in mouse model outcomes, we aim to improve the reliability of these studies and their applicability to human medicine.

Our approach involves a qualitative analysis of current experimental designs, protocols, control measures, and sample sizes. We investigate how confounding variables in these models lead to inconsistent data, focusing on factors like mouse model type, susceptibility to specific cancer subtypes, genetic background, and environmental conditions.

INTRODUCTION

- Colorectal cancer (CRC) is second leading cause of cancer death in United States
- However, there is a 92% failure rate of translation from animal to human

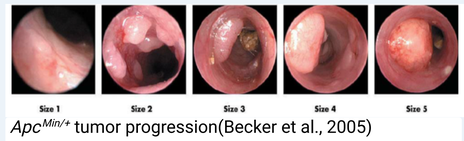


- Study done by Norman in 2019 shows low success rate for drugs that advance beyond preclinical and clinical trials

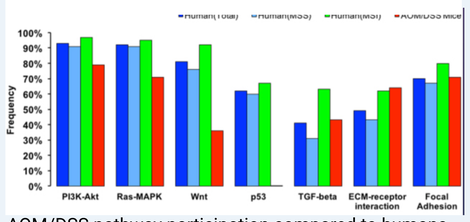
METHODS

- A systematic review was conducted through evaluating through literature studying colorectal cancer in mice and their methods to try and understand causes for study variation in mouse models
- Special attention was given to the *APC*$^{Min/+}$, AOM/DSS, and Cre-ER^{T2} models and variations within those
- Possible variations were split into three categories : Model Type Related , Genetic Background Related, and Environmental differences.
- Literature was consulted to understand the mechanism behind the differences and how they can affect experimental outcomes and preclinical conclusions.

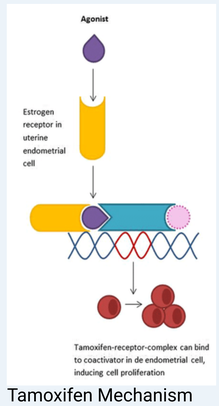
RESULTS



Apc$^{Min/+}$ tumor progression(Becker et al., 2005)



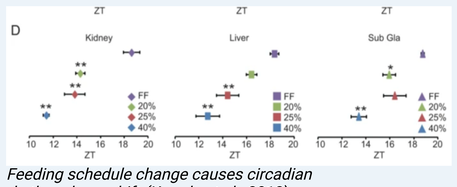
AOM/DSS pathway participation compared to humans (Pan et al., 2017)



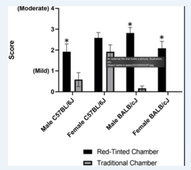
Tamoxifen Mechanism (Schuurman et al., 2019)

- *Apc*$^{Min/+}$ model has been shown to produce more tumors in small intestines than colon which causes mice to die from intestinal blockage before metastasis can be observed
- AOM/DSS pathway observed to not activate same cellular pathways in mice as humans during colorectal cancer incidences
- Tamoxifen, acting as a partial nonsteroidal agonist binds to estrogen receptors instead of estrogen indicating possibility that tamoxifen is causing unintended phenotypic expression

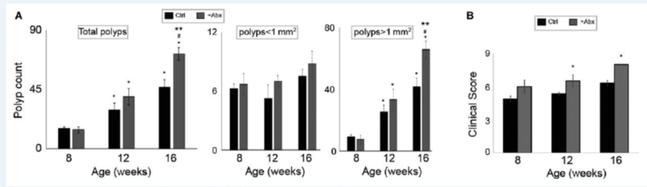
- Changing feeding schedule/time on mice causes circadian rhythm phase shift, impacting endocrine signal fluctuations that could cause variations in tumorigenesis
- Mouse whose gut microbiome was altered while still developing intestinal tumors had increased polyp count and sizing as a result.
- External Environmental Factors such as cage color can also induce anxiety in mice contributing to inflammation and inflammation based responses which could further impact tumor development.



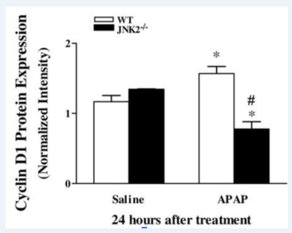
Feeding schedule change causes circadian rhythm phase shift (Kuroda et al., 2012)



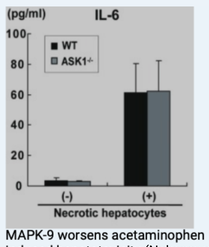
Cage Color affects Mouse Anxiety (Sasaki et al., 2016)



Exposure to gut-targeting antibiotics causes polyp phenotypical expression change (Kaur et al., 2018)



MAPK-9 helps relieve acetaminophen induced hepatotoxicity (Bourdi et al., 2008)



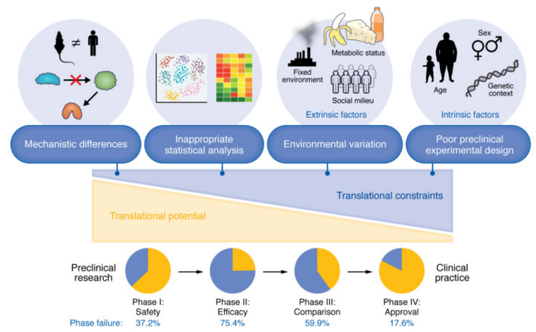
MAPK-9 worsens acetaminophen induced hepatotoxicity (Nakagawa et al., 2008)

Acetaminophen-induced hepatotoxicity case study

- Bourdi in 2008 determined the MAPK-9 pathway is hepatoprotective while Nakagawa in the same year showed that the pathway is hepatotoxic.
- Differing results caused due to strain difference where Bourdi was using B6J mice and Nakagawa was using B6N thus showing how genetic background can significantly vary phenotypic expression and physiological response

CONCLUSION

- Numerous sources of variance in mouse model experimental design is causing a low translational success rate in preclinical models
- Using different mouse models of colorectal cancer mandates multi-model testing to ensure results are not strain specific.
- Different genetic backgrounds in a trial mandates the use fo robustness testing to ensure that results observed are not background specific
- There is a great importance in keeping consistent environmental conditions in mouse models as external changes and stimuli can cause phenotypical manifestation.



Research done by Dr. Mcgill and Dr. Threadgill showing how translational potential can vary with constraints.

ACKNOWLEDGEMENTS

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