Background Breast cancer is a complex disease which is defined by an intrinsinc heterogeneity at the histopathological and molecular levels, as well as in response to therapy. It remains the second leading cause of cancer death among women worldwide despite advances in screening, detection and new therapeutic options. Therefore, it is important to establish relevant preclinical mouse models to study new therapeutics and tumor biology. Genetically engineered mouse models (GEMMs) have been developed in order to understand the molecular, biochemical and cellular functions of oncogenes or tumor suppressor genes. However, the application of GEMMs is constrained due to the spontaneous nature of tumor onset and progression and high cost of breeding. Homograft tumor models, which are derived from and retain the histopathological and molecular features of GEMMs, can be used as faithful surrogates of human tumors.

Methods We generated a series of homograft tumor models from GEMMs overexpressing human epidermal growth factor receptor 2 (HER2, also known as ERBB2) or polyomavirus middle T antigen (PyMT) driven by the mouse mammary tumor virus (MMTV) promoter, or Simian Virus 40 T-antigen (SV40 Tag) under the promotion of the rat prostate steroid binding protein (C3(1)), which are commonly used GEMMs in preclinical breast cancer research. 1, 2 Models were generated by transplanting the mammary tumors into donor animals. Furthermore, we characterized the homograft tumors through histopathological analysis, immunohistochemical analysis, and immune profiling, as well as immunotherapeutic, cytotoxic and targeted therapy.

Results Nine breast cancer homograft models were developed from MMTV-ERBB2, MMTV-PyMT and C3(1)-Tag GEMMs, including six hormone receptor negative and HER2 positive models (mBR9015, mBR9026, mBR9027, mBR9028, mBR9029, mBR9030), one hormone receptor positive and HER2 negative model (mBR6174) and two triple negative models (mBR6004, mBR9014). Immune profiling of six models showed enriched macrophage infiltration in the tumor microenvironment. Immunotherapy treatment with anti-mPD-1 and anti-mCTLA-4 produced tumor growth inhibition (TGI) of 98% and 110%, respectively, in the triple negative model mBR9014, accompanied by tumor regression. HER2 targeted treatment with lapatinib produced robust response with TGI ranging from 48% to 97% in one HER2 negative and two HER2 positive models. Varying response to the cytotoxic treatments was observed among different models, with cisplatin producing robust response of TGI over 80% in all five of the tested models.

Conclusions We have generated and characterized a series of mouse breast cancer homograft models from GEMMs to facilitate both mechanistic investigation and preclinical testing of novel therapeutics.

Ethics Approval Animal experiments were conducted in accordance with animal welfare law, approved by local authorities, and in accordance with the ethical guidelines of Crown-Bio (Taicang).

REFERENCES

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0738
Conclusions Several human esophageal adenocarcinoma models were successfully established, primarily from endoscopic biopsy of treatment-naïve patients as neoadjuvant therapy proved to be a significant barrier. These models will be useful to explore GUCY2C-directed CAR-T cell therapies and other novel therapies targeting intestine-like esophageal cancer, prior to testing in early-phase clinical trials.

Acknowledgements The authors thank the Translational Research & Pathology Core Facility and the Office of Animal Resources at Thomas Jefferson University for their continued support to make this research possible. The authors would also like to thank the Clinical Research Unit at Thomas Jefferson University for their assistance in the collection of patient specimens. This work was supported by a DeGregorio Family Foundation Award and by the Department of Defense Congressionally Directed Medical Research Programs (W81XWH-17-1-0299, W81XWH-191-0263, and W81XWH-19-1-0067) to AES. SAW was supported by the National Institutes of Health (NIH) (R01 CA204881, R01 CA206026, and P30 CA56306), the Defense Congressionally Directed Medical Research Program W81XWH-17-PRCRP-TTSA, and Targeted Diagnostic & Therapeutics. SAW and AES were also supported by a grant from The Courteney Ann Dionat Memorial Foundation. SAW is the Samuel M.V. Hamilton Professor of Thomas Jefferson University. AZ and MC were supported by NIH institutional resources at Thomas Jefferson University for their continued support to make this research possible. The authors thank the Translational Research & Pathology Core Facility and the Office of Animal Resources at Thomas Jefferson University for their continued support to make this research possible.

Ethics Approval The study was approved by the Thomas Jefferson University Institutional Review Board (#18D.495) and Institutional Animal Care and use Committee (#01529).

REFERENCES

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0739

BIOMARKERS DIVERGING BETWEEN TUMOR MUTATION BURDEN AND MICROSATELLITE INSTABILITY

Jason Ding*, 1Nihir Patel. 1Mountain Lakes High School, Mountain Lakes, NJ, USA; 2Admera Health, South Plainfield, NJ, USA

Background DNA repair is a critical process to maintain DNA integrity. It is conducted by distinct pathways of genes, many of whose alterations are thought to occur in genomic instability and hypermutability, ultimately contributing to tumorigenesis. Tumor Mutation Burden (TMB) and Microsatellite Instability (MSI) are considered as efficacy biomarkers for immunotherapy.1,2 However, there has been little characterization of the association between DNA repair genes and TMB/MSI in cancer. This study aims to further understand DNA repair genes and evaluate the contribution of their alteration to TMB and MSI.

Methods We systematically analyzed 282 DNA repair genes involved in 20 DNA repair pathways. These genes were evaluated for mutations based on 274 sequenced colorectal tumor samples from the TCGA database. The functional impacts of these mutations were analyzed, and only damaging mutations were used for the subsequent analysis. The most frequently mutated genes were identified. The association between the damaging mutations and TMB/MSI status was calculated for each gene, and the significant genes were subject to further pathway enrichment analysis. We also compared the gene expression between TMB high and low as well as between MSI-H and MSI-L/MSS for each gene based on their RNAseq data. The potential associations with TMB/MSI high phenotypes were evaluated.

Results 94 genes were identified to be significantly mutated in TMB high, including all of the 26 genes that were significant in MSI-H. The genes are enriched in multiple pathways, including Fanconi anemia, Base excision repair, and Mismatch repair. At the expression level, 28 genes are significantly downregulated in TMB high samples, while 35 genes in MSI-H, suggesting that the inactivation of these genes might be mediated by epigenetic abnormalities (figure 1). 10 genes,