American Association for Cancer Research®

Abstract Number: LB181

USING CAUSAL AI *IN-SILICO* PATIENT MODEL TO INFER CANCER CELL GENE DEPENDENCY IN MULTIPLE MYELOMA

BRANDON NATHASINGH[1], DEREK WALKAMA[1], LAUREL MAYHEW[1], KENDALL LOH[1], JEANNE LATOURELLE[1], BRUCE CHURCH[1], YAOYU E. WANG[1]

1. Aitia, Somerville, MA

Contact: ywang@aitiabio.com

AITIA

SUMMARY

Causal inference network models are particularly suited to facilitate therapeutic intervention studies by inferring the molecular causal structure from multimodal data. Here, we developed a multiple myeloma (MM) Digital Twin model of overall survival (OS) to perform full transcriptome *in-silico* loss-of-function experiments. We compared the results to MM cell lines CRISPR knock-out data from DepMap[1] to show high concordance. The model also identifies additional dependent genes and provides potential mechanisms of action. This demonstrates *in-silico* AI causal modelling is a powerful tool for exploring cancer cell vulnerability from patient data to advance target discovery.

AIMS

We aim to demonstrate that our multiple myeloma Digital Twin model can identify cancer cell dependent genes with *in-silico* knockdown experiments, identify response biomarkers, and suggest mechanisms of action.

RESULTS

The *in-silico* loss-of-function experiments on the MM Digital Twin model identified 102 OS driver genes that causally drive patient overall survival. Most of the coding genes are found to be MM-Dependent in DepMap. **PHF19**, a gene known to control MM cell proliferation[2], was found to be non-dependent in the DepMap but was identified as an OS driver by our model.

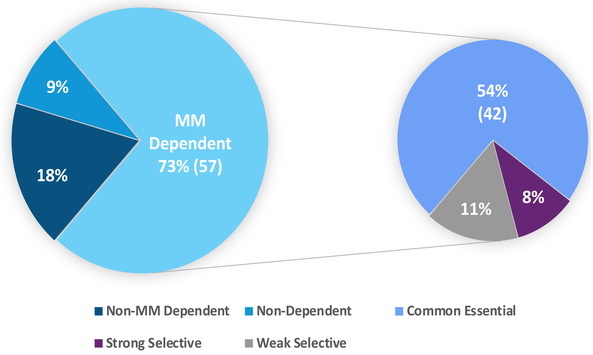

Figure 2: DepMap Annotation of OS Driver Genes. 73% (57/78, p<2.2e-16, OR=9.6) of the coding genes are dependent in MM cell lines, with 42 common essential, 6 strong selective and 9 weak selective genes. The remaining 21 OS driver genes, 14 (66%) are non-MM Dependent.

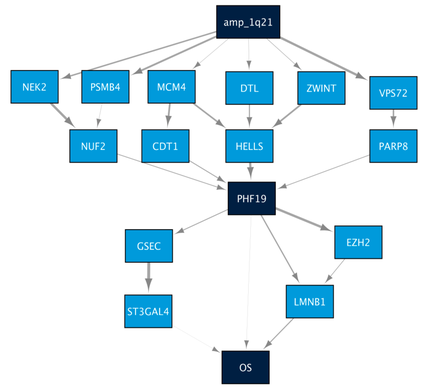

Figure 3: Model Topology around PHF19: The PHF19 local network suggests 1q21 amplification causally affects PHF19 and patient OS.

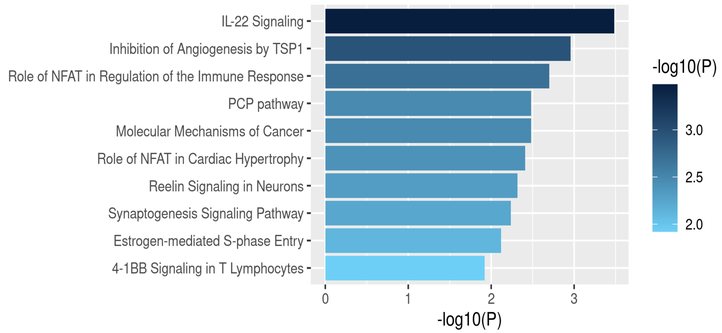

Figure 5: Biological pathways driven by PHF19: 162 downstream genes are enriched in report processes in cell proliferation and angiogenesis[3].

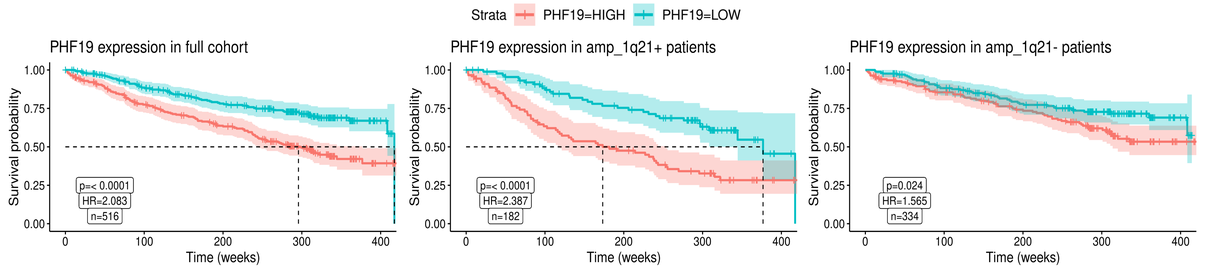

Figure 4: Response biomarkers for PHF19: Kaplan Meier plots for conditioned subpopulations stratified by median PHF19 expression.

METHODS

We constructed an *in-silico* multiple myeloma (MM) patient causal model of overall survival (OS) based on transcriptomic expression, clinical, and genomic alteration data from Multiple Myeloma Research Foundation (MMRF) CoMMpass dataset (IA19). The causal inference model for the MM Digital Twin was constructed using Aitia's REFS™ platform (Figure 1), then *in-silico* loss-of-function experiments were performed through counterfactual simulations of all gene expressions to assess their causal effects on patient overall survival (OS) and identify the OS driver genes.

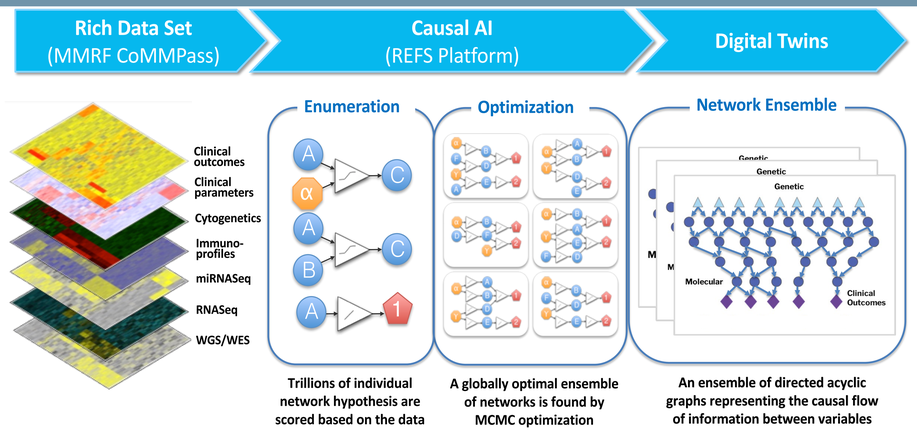

Figure 1: Machine Learning Methods (REFS™): REFS™ workflow used to build the MM in-silico Digital Twins. After filtering for data quality and availability, we included 516 patients in the model, with 60% being hyperdiploid.

Dependency and Functional Analysis

The OS drivers were annotated using the DepMap (v.22Q4) MM cell lines data as follows:

- **MM-Dependent**: genes required for MM cell line survival
- **Non-MM Dependent**: genes required for some cancer cell line survival but not MM
- **Non-Dependent:** genes not found to be required for cancer cell line survival

Downstream genes of OS drivers were analyzed for enriched functional pathways using Ingenuity Pathway Analysis tool (IPA).

CONCLUSIONS

In this study, we demonstrate Aitia Digital Twins model can accurately screen for cancer genetic vulnerabilities in multiple myeloma and reveal their associated biomarker as well as their potential functional mechanisms. The Aitia Digital Twin model is a powerful tool in target discovery and biomarker identification and can be readily applied to other cancer types.

REFERENCES/CONTACT

1. Tsherniak A, et al. Defining a Cancer Dependency Map. Cell. 2017 Jul 27;170(3):564-576.e16.
2. Ren Z, et al. PHF19 promotes multiple myeloma tumorigenicity through PRC2 activation and broad H3K27me3 domain formation. Blood. 2019 Oct 3;134(14):1176-1189.
3. Jain P, et al. PHF19 mediated regulation of proliferation and invasiveness in prostate cancer cells. Elife. 2020 Mar 10;9:e51373.