Kelly Regan-Fendt
PhD Candidate

“Integrative Network and Transcriptomics Approach Enables Computational Drug Repurposing and Drug Combination Discovery in Melanoma”

March 9, 2018
Lincoln Tower 245
9:00 AM
VITA

10/5/1988 ............................................ Born - Oak Park, IL

2011 ......................................................... B.A., Biology, University of Chicago

2012 ......................................................... MD, PhD. Candidate, The Ohio State University

COMMITTEE MEMBERS

Philip R. O. Payne, PhD, Advisor

William E. Carson, MD, Co-Advisor

Fuhai Li, PhD

Jeffrey Parvin, PhD
ABSTRACT

Systems biology perspectives are crucial for understanding the pathophysiology of complex diseases and hold great promise for the discovery of novel treatment strategies. Drug combinations show great promise to improve durability and reduce resistance to available first-line therapies in a variety of cancers; however, traditional drug discovery approaches can also be prohibitively cost and labor-intensive. Computational methods are needed to efficiently model complex interactions of drug target pathways and identify mechanisms underlying drug combination synergy. As an exemplar of a disease in which combination therapies demonstrate efficacy in genomic-specific contexts, we explore malignant melanoma, the deadliest form of skin cancer, which has the most mutated genome of all known cancers.

In this study, we employ a novel computational approach, SynGeNet (Synergy from Gene expression and Network mining) to derive drug combination predictions through a systems biology perspective. Briefly, the SynGeNet approach first models disease signaling networks via the integration of genomics, transcriptomics and protein-protein interaction to map “signal flow” from a set of disease-causal or highly mutated “root” genes. Drug pairs are first identified that can reverse the gene expression patterns characterizing the disease signaling network and ranked based on drug targets’ distribution within the network. Drug combination candidates are hypothesized to have a maximal effect on the overall disease signaling network that both i) alter composite gene expression signals of the disease network and ii) target highly central or influential network nodes.

Due to the heterogeneous genomic landscape of melanoma, we applied SynGeNet to network models of melanoma tumors driven by distinct driver mutations: \textit{BRAF}, \textit{NRAS}, \textit{NF1}, and triple wild-type. We validated synergistic drug combinations predicted by our method across different genomic subtypes using results from two independent high-throughput drug screening studies and demonstrated that our method could outperform two publicly
available transcriptomics-based drug combination prediction tools. Furthermore, we address several assumptions of model, including empiric parameter testing, assessment of robustness to noise and model component deconstruction. Our analyses demonstrated that modeling unique signaling networks for each subtype via integrating genomic and transcriptomic data performed better than using either data type alone, random signaling network interactions or generalized network models of melanoma.

Finally, we prospectively validated a novel drug combination for \textit{BRAF}-mutant melanoma that was top-ranked by our approach, vemurafenib (BRAF inhibitor) + tretinoin (retinoic acid receptor agonist), using both \textit{in vitro} and \textit{in vivo} models of \textit{BRAF}-mutant melanoma. Through RNA-seq analysis of cell lines post-drug treatment, we confirmed molecular mechanisms predicted by the SynGeNet method, including reversal of most gene expression signals at the network level, as well as at an individual gene level for the most “central” (i.e. topologically important) genes within the \textit{BRAF} melanoma signaling network. We also applied a random walk with restart (RWR) to define highly impacted gene sub-networks within the signaling networks by a drug pair to prioritize pathways underlying mechanisms of action for drug combinations. These findings demonstrate that our approach may be applicable to a wide range of disease domains, and importantly, can model disease signaling processes in precision-medicine contexts.
RECENT ABSTRACTS AND PRESENTATION


Regan K, Reyes R, Yu L, Jacob ST, Payne PRO, Motiwala T. “Drug repurposing for hepatocellular carcinoma enabled via transcriptomics data from experimental models of sorafenib resistance.” Oral Presentation: Biomedical Sciences Graduate Program Retreat, The Ohio State University College of Medicine, Columbus, OH. December 2016.

Recent Publications


AWARDS AND HONORS

2014-2017 NIH National Library of Medicine CTRIP Fellowship
2017          Best Student Paper award, AMIA TBI Joint Summits
2017          Ray Travel Award, OSU
2016          Best Research Essay Award, Landacre Honor Society
2016          OSUWMC Trainee Research Day Poster Travel Award
2016          OSUCOM Medical Alumni Society Student Grant
2016          Hayes Graduate Research Forum Oral Speaker Nomination
2016          Molecular Med Tri-Conference Oral Speaker Nomination
2016          Molecular Med Tri-Conference Student Fellowship
2016          Landacre Honor Society Inductee
2015          Sigma Xi Inductee
2015          Phi Kappa Phi Inductee
2013          MD/PhD Leadership and Academic Achievement Award
2012          Overall Poster Winner, AMA Interim Meeting
2012          Clinical Outcomes & Healthcare Improvement category
Poster Winner, AMA Interim Meeting

FUTURE PLANS

I will return to medical school to complete my medical training, after which I plan to pursue a research residency. In my future career, I hope to practice and improve medicine through translational research.