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A systems pharmacology approach to higher order drug combinations in prostate cancer

H Alexander Ebhardt
Systems Biology Ireland- UCD, Ireland

Introduction: Healthy aging in men coincides with regular screening of their prostate as malignancies may develop at any time. Malignancies in prostate start as local disease but aggressive tumour development might lead to a non-localized metastatic disease state (mPCa). The unmet clinical need remains i.e. to eradicate mPCa and return men to a healthier.

Methodology: We used evolutionary modelling to estimate the number of drugs necessary to eradicate mPCa. Then we carried out a perturbation study in which we treated mPCa models with six drugs in single and all double drug combinations. Changes to the proteome were quantified using targeted proteomics and reverse protein arrays. This analysis identified a number of proteins and signal transduction pathways to be targeted in a triple drug combination. Commercially available inhibitors had uncertain binding specificity against the target and we used structure-based drug design to assess their specificity. Following our analysis, triple drug combinations were tested in a mPCa model.

Results: Due to the tumour burden and heterogeneity in mPCa, more than two drugs are required to obtain a reduction in tumour mass. Most likely triple combination therapy will be necessary to overcome the emergence of drug resistance and return men to healthier state. Identifying ways in which tumours block the action of two drugs is a way of prioritizing drug targets for triple combinations.

Conclusions: The combined approach of *in silico* modelling and systems pharmacology resulted in a promising new drug combination to treat mPCa.

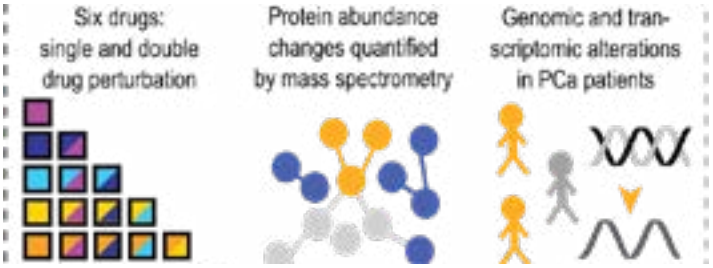

Figure1. Description: Project overview

Recent Publications:

1. A Root and H A Ebhardt (2018) A two-drug combination simulation study for metastatic castrate resistant prostate cancer. The Prostate 78(15):1196-1200.
2. H A Ebhardt (2018) Systems pharmacology using mass spectrometry identifies critical response nodes in prostate cancer. NPJ Syst. Biol. Appl. 4:26.

Biography

H Alexander Ebhardt obtained his PhD in Molecular Biology and Biochemistry from Simon Fraser University, British Columbia, Canada investigating endogenous and exogenous small RNAs in a virally infected system (*Proceedings of the National Academy of Sciences of the United States of America* 2005). He is presently a Junior Group Leader at Systems Biology Ireland and continues his research in the area of prostate cancer. RNA proteins play a vital role in the life cycle of biological systems hence, he expanded his expertise to include quantitative mass spectrometry. At ETH Zurich, Switzerland, he applied his new gained analytical expertise to prostate cancer. Using a systems pharmacology approach his research aimed at identifying new protein targeted for higher order drug combination therapy for metastatic castrate resistant prostate cancer.

h.a.ebhardt@ucd.ie