Next generation protein biomarker signature in blood for early detection of colorectal cancer

Christos Fotis[1,2], Nikolaos Meimetis[3], Nikolaos Tsolakos[1], Athanasios Stamogiannos[1], Vaia Pliaka[1], Ioannis Temponeras[1], Eleni Koukoulioti[4], Elli Karatza[4], Pinelopi Antonopoulou[4], Krystalina Kapantai[4], Georgia Anagnostou[4], Douglas A. Lauffenburger[3], Ioannis S. Papanikolaou[4], Leonidas Alexopoulos[1,2]

1)Protavio Ltd, Demokritos Science Park, Athens, Greece

2)Biomedical Systems Laboratory, National Technical University of Athens, Athens, Greece

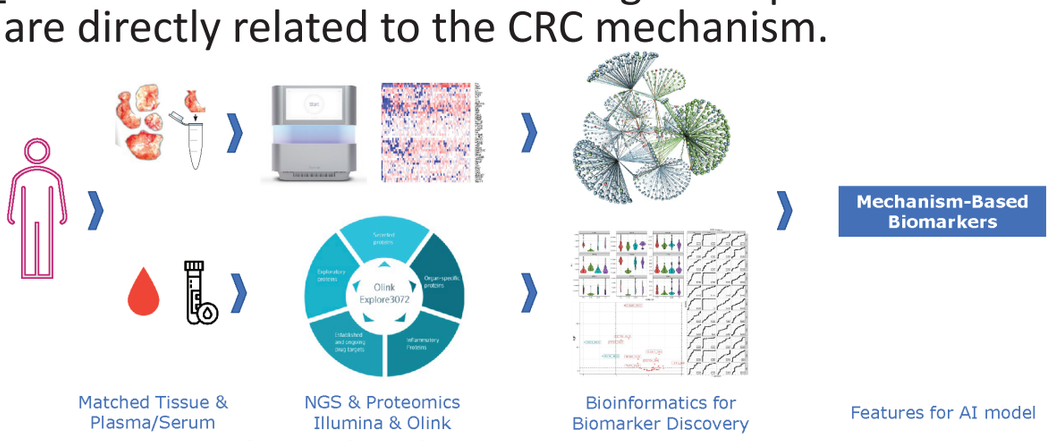
3)Department of Biological Engineering,Massachusetts Institute of Technology, Cambridge, MA, USA,

4)Hepatogastroenterology Unit, Second Department of Internal Medicine- Propaedeutic, Medical School, National and Kapodistrian University of Athens, Attikon University General Hospital, Athens, Greece

Abstract

Importance: Colorectal cancer is the second leading cause of cancer-related deaths in Europe and the United States.

Aim: Discover novel blood-based diagnostic protein biomarkers that are directly related to the CRC mechanism.



Discovery Clinical Cohort

Group	Participants	Age (median)	Age (IQR)	Sex (%)
CRC	65	65.0	15.0	Female: 45.4 Male: 54.6
AA	106	65.0	13.0	Female: 40.9 Male: 59.1
NAA	50	63.5	10.8	Female: 47.6 Male: 52.4
Healthy	75	56.5	17.3	Female: 54.1 Male: 45.9

- CRC = Colorectal cancer patients
- AA = Advanced Adenomas
- NAA = Patients with non neoplastic findings
- Healthy = Patients with no findings

Analysis Pipeline

Initial Exploratory Analysis
e.g. Clustering,Covariate Analysis
Blood proteomics data of 296 participants

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Biomarkers Discovery
1. Differential protein analysis
2. Important proteins in Machine Lerning modeling (e.g. Elastic Net)
3. ROC analysis of signle proteins

Biomarkers Prioritization
1. Limit of Detection Filtering
2. Filtering using Normal range in UKBiobank
3. Significant trend in clinical groups

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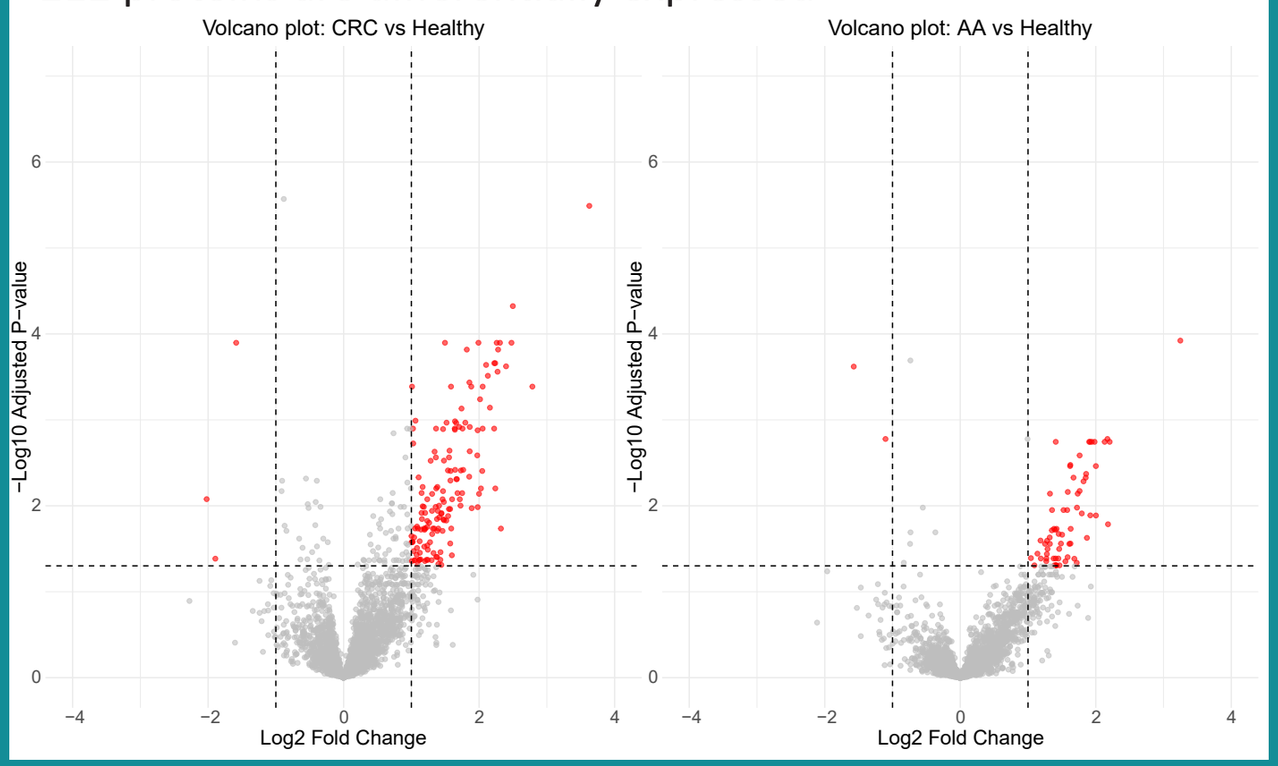
Biomarkers Evaluation
1. Optimal combination of biomarkers
2. Final evaluation of panel of protein biomarkers

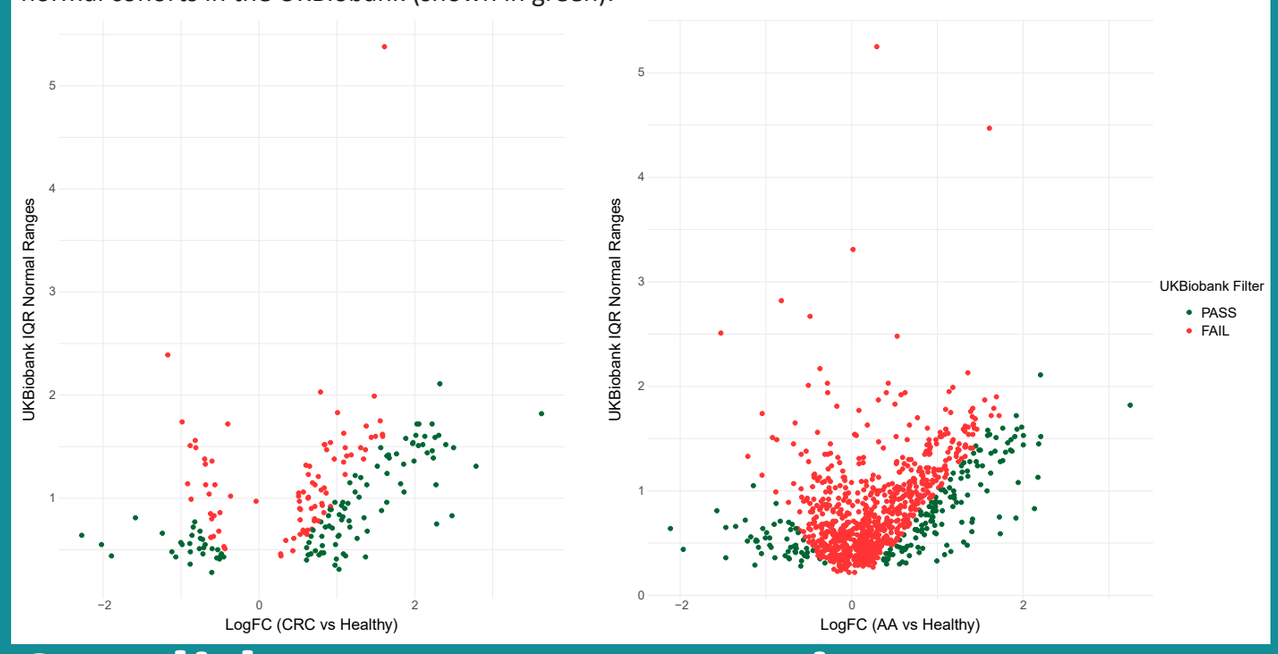
Differential expression analysis

*212 proteins are differentially expressed



Biomarker prioritization criteria

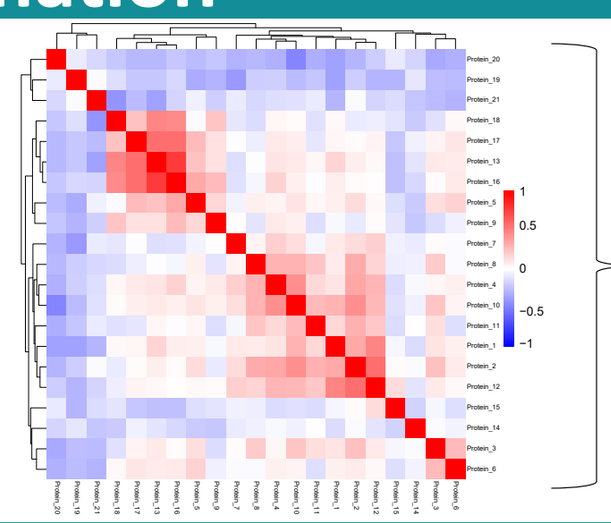
One prioritization criterion is based on the comparison of biological effect size with the Normal ranges from the UK Biobank. We applied this criterion in order to ensure that the final multiplex assay can potentially achieve greater specificity. We select for proteins with a log(FC) greater than the interquartile range in normal cohorts in the UKBiobank (shown in green).



The final model has high performance across all groups

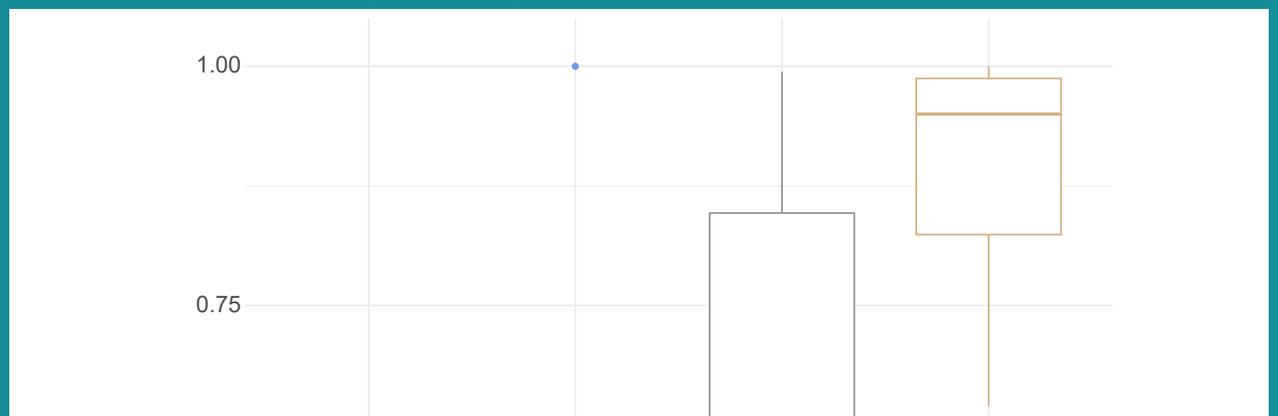
Comparison	AUC (%)	Sensitivity (%)	Sensitivity 95% CI	Specificity (%)	Specificity 95% CI
CRC vs Normal	95.9	98.1	90.1-100.0	93.1	77.2-99.2
SI vs Normal	96.9	100.0	71.5-100.0	93.1	77.2-99.2
SII vs Normal	97.6	100.0	75.3-100.0	93.1	77.2-99.2
SI/SII vs Normal	97.3	100.0	85.8-100.0	93.1	77.2-99.2
AA vs Normal	78.0	50.0	37.0-63.0	93.1	77.2-99.2
HGD vs Normal	74.7	43.5	23.2-65.5	93.1	77.2-99.2
CIS vs Normal	66.4	50.0	6.8-93.2	93.1	77.2-99.2
AA10 vs Normal	85.8	61.1	35.7-82.7	93.1	77.2-99.2
V vs Normal	74.1	50.0	21.1-78.9	93.1	77.2-99.2

Candidates capture unique information



Performance of 12-plex assay and single biomarkers for CRC detection

Predicted probabilities separate different groups



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