Plasma-Based Metabolic Profiling in Metastatic Gastrointestinal Stromal Tumors (mGIST)

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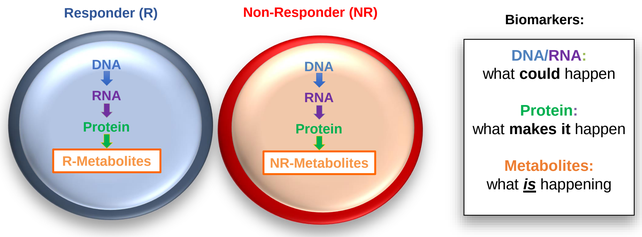
WHAT IS THE PROBLEM?

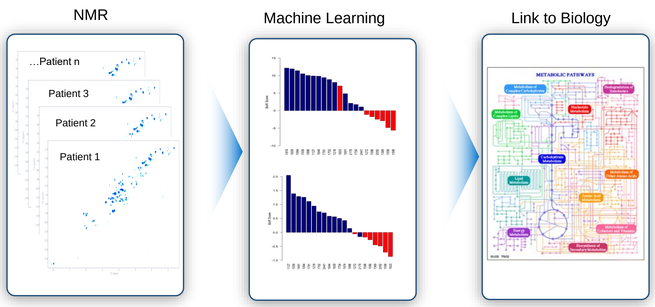
Discovery of oncogenic mutations as targets for cancer therapy revolutionized treatment of GIST and other cancers. However, nearly all patients ultimately progress either through **intrinsic resistance (IR) or acquired resistance (AR)** to therapy emphasizing the need for **biomarkers** to assess cancer prognosis and factors associated with benefit of cancer therapies.

THE OLARIS BOR SOLUTION COMBINES METABOLOMICS & MACHINE LEARNING

Altered metabolism is a hallmark of cancer, enabling tumors to proliferate, survive and metastasize. By measuring the complete set of metabolites in an individual (metabolome) it is possible to identify biomarkers that correlate with disease status, prognosis, and therapeutic response.



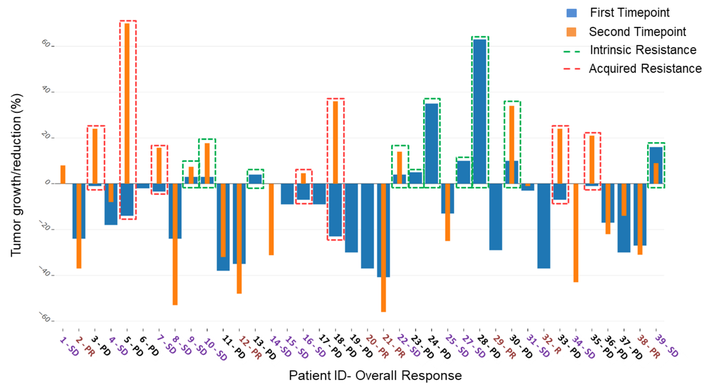
We detect and quantify **metabolites** from hundreds of patient biofluid samples (blood and/or urine). Using **NMR** and **MS** based metabolomics and **machine learning** we identify **"biomarkers of response" (BoR)** which can predict disease progression and/or treatment response.



METHODS

Untargeted multi-dimensional NMR and MS-based machine learning (ML) metabolomic analysis was performed on serial plasma samples collected from 39 patients with advanced GIST at baseline (BL) and during experimental systemic therapies including a first time-point (FT) after ~1 ± 0.25 months and second time-point (ST) after ~8 ± 6 months. Results were compared to clinical outcomes, wherein a Kruskal-Wallis, a non-parametric one-way analysis of variance was used to test for significant differences. Only significant features were used for additional ML analysis. Samples were stratified by sex and mutation status.

PATIENT CHARACTERISTICS



Intrinsic resistance (IR) was defined as patients on treatment less than 6.5 months and with tumor growth (TG) at FT. Acquired resistance were those patients with tumor reduction (TR) of ≥ -5% at FT followed by an increase in TG of ≥15% at ST. Partial response (PR), stable disease (SD) and progressive disease (PD) were defined according to RECIST criteria.

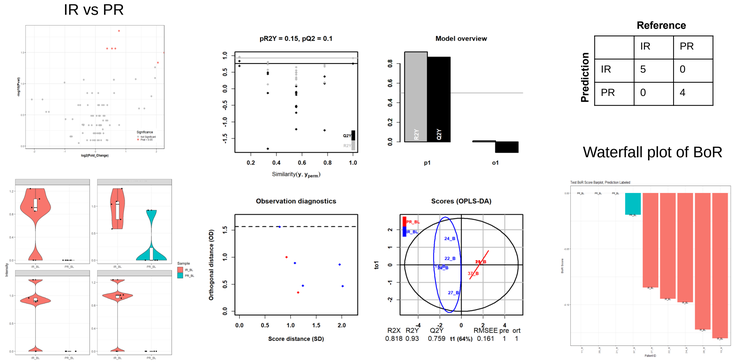
METABOLITE LEVELS PREDICT RESPONSE

TRAINING

BL Male Differential Metabolites IR vs PR

OPLS-DA Model

Random Forest Model

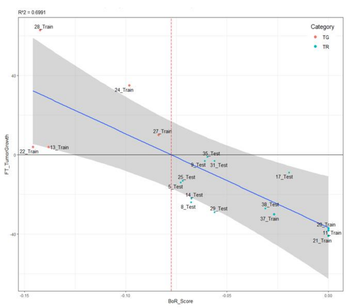


Waterfall plot of BoR

Using the top differential features we constructed ML models to differentiate male IR (N=4) vs PR (N=5) patients at BL. We plotted the Olaris® BoR Score against tumor growth for the training data and observed a strong linear correlation (R^2=0.6991) and were then able to **accurately predict TG or TR for all other BL male samples (N=10).**

BL BoR Score Correlates With Tumor Growth For Test Samples

BoR Score vs Tumor Growth at BL for Training & Test dataset



BoR Score, TG prediction for Train and Test Samples at BL

Patient ID	Train Test	Category	BoR Score	FT Tumor Growth	TG Prediction	Lesion
13	Train	TG	-0.13809	4	-	Yes
22	Train	TG	-0.14580	4	-	
24	Train	TG	-0.09836	35	-	
27	Train	TG	-0.08383	10	-	
28	Train	TG	-0.14232	63	-	
11	Train	TR	0.00000	-38	-	
20	Train	TR	0.00000	-37	-	
21	Train	TR	0.00000	-40.8	-	
37	Train	TR	-0.02680	-30	-	
5	Test	TR	-0.07286	-14	-2.23 ± 16.84	
8	Test	TR	-0.06777	-24	-4.64 ± 16.85	
9	Test	TR	-0.06102	-3	-7.83 ± 17.04	
14	Test	TR	-0.06752	-22	-4.76 ± 16.85	
17	Test	TR	-0.01944	-9	-27.49 ± 22.00	Yes
25	Test	TR	-0.07186	-13	-2.71 ± 16.83	
29	Test	TR	-0.05622	-29	-10.10 ± 17.29	
31	Test	TR	-0.05618	-3	-10.12 ± 17.30	Yes
35	Test	TR	-0.05973	-1	-8.44 ± 17.10	
38	Test	TR	-0.03116	-27	-21.95 ± 20.07	

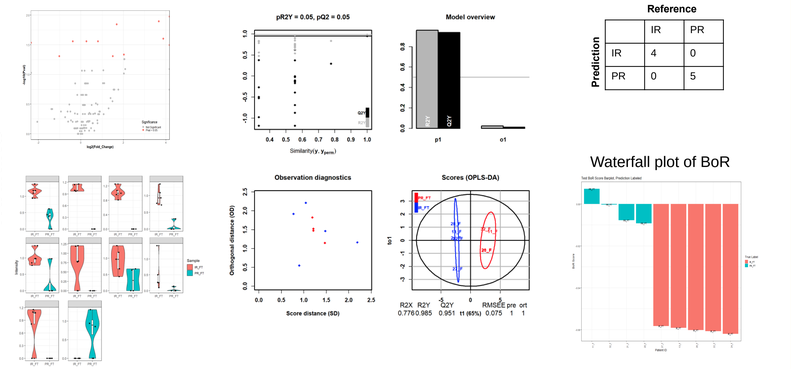
METABOLITE LEVELS PREDICT RESPONSE

TRAINING

FT Male Differential Metabolites IR vs PR

OPLS-DA Model

Random Forest Model

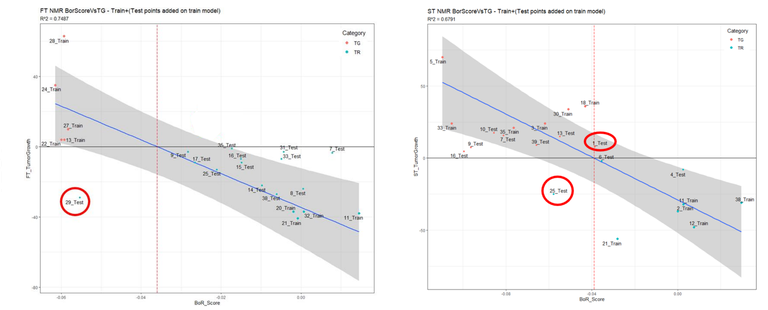


Waterfall plot of BoR

FT & ST BoR Score Correlates With Tumor Growth For Test Samples

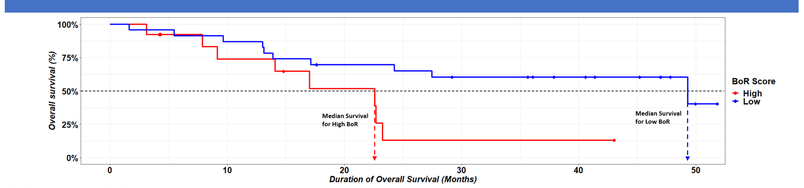
BoR Score vs Tumor Growth at FT for Training & Test dataset

BoR Score vs Tumor Growth at ST for Training & Test dataset



Using the top differential features we constructed ML models to differentiate male IR (N=4) vs PR (N=5) patients at FT and the PD (N=5) and PR (N=10) patients at ST. We plotted the Olaris® BoR Score against tumor growth for the training data and observed a strong linear correlation (R^2=0.749 at FT and R^2=0.679 at ST) and were then able to predict TG or TR for additional FT test samples (N=14) and ST test samples (N= 10) with **92% and 80% accuracy** respectively.

METABOLITES CORRELATE WITH OS



Kaplan-Meier curves demonstrates that from a pre-dose plasma sample the Olaris® BoR score can be used to assess prognosis. Patients with high and low BoR have median overall survival (OS) of **22.60 months and 49.33 months respectively.**

CONCLUSION

Comprehensive metabolomic profiling of serially collected plasma is feasible and detects metabolic signatures associated with therapeutic response in advanced GIST. Upon validation in larger patient cohorts, the BoR signatures could be useful to design optimal treatment paradigms.