Development of a Biomarker-driven patient selection strategy for AsiDNA^{TM} treatment

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Abstract

Purpose: Accurate evaluation and prediction of response to anti-cancer treatment remain a great challenge. Stratification biomarkers are of great value to identify responders or non-responders to a specific drug, or even to distinguish between early and delayed responses. In this study, we identified a gene signature to predict AsiDNA treatment efficacy in patients.

Experimental design: The first step of this study consisted on the analysis of gene expression profile in a set of 12 Breast cancer cell lines. Genes retrieved from correlation analysis between sensitivity to AsiDNA and transcriptomes were used to create a gene signature predicated on the upregulation of positively correlated genes and the down regulation of negatively correlated genes (the AsiDNA sensitivity signature - AsiSS) using the UCSC Xena platform for data visualization. The AsiSS was used to sort the TCGA Breast Cancer (BRCA) patient cohort, DNA repair gene expression and cell lines from the CCLE (1100 cell lines) into rank orders, in order to retrieve a gene set highly predictive of response to AsiDNA.

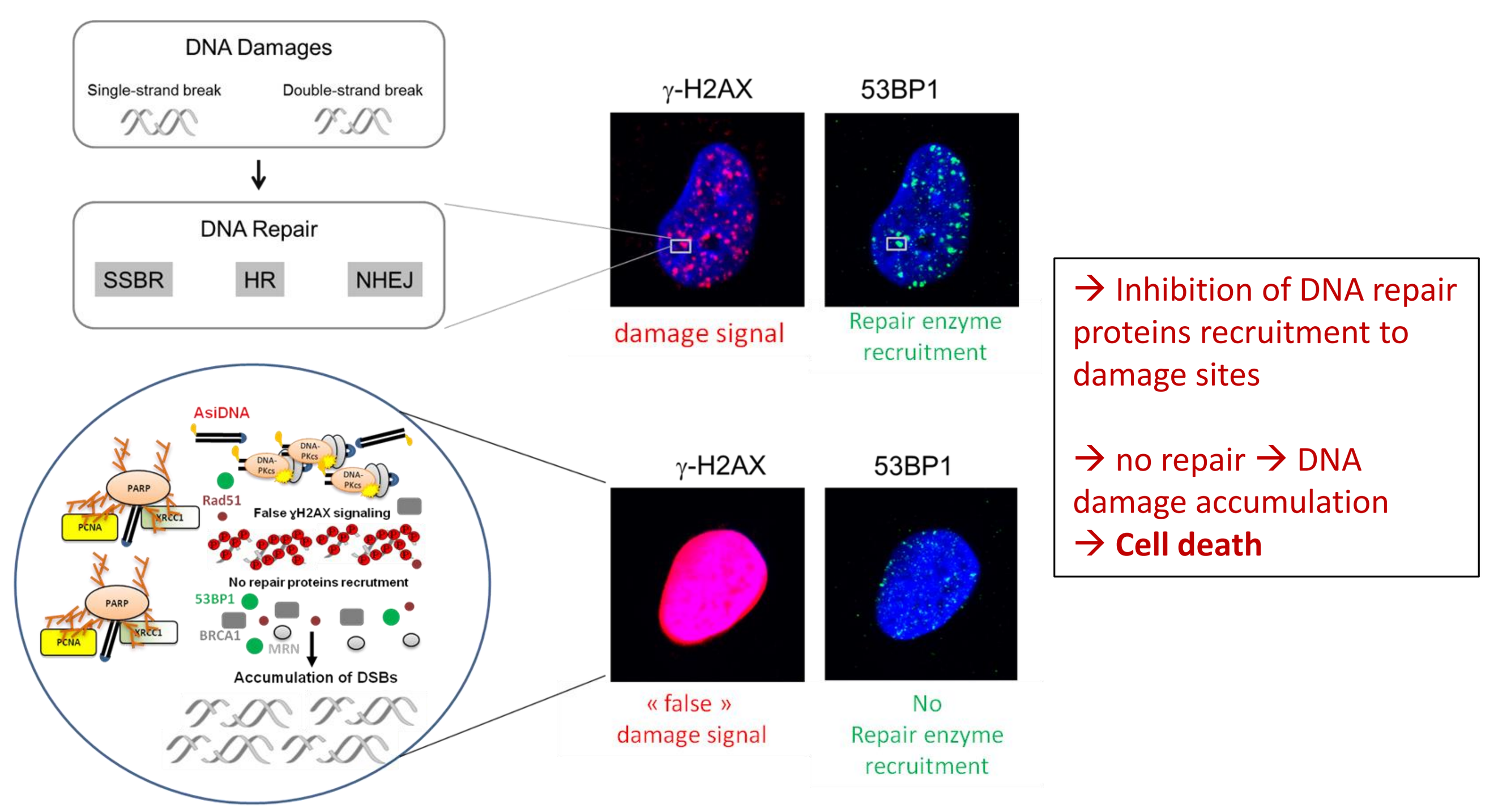
Results: A list of genes the most strongly correlated with survival to AsiDNA was compiled. 39 genes showed expression profiles positively correlated with survival to AsiDNA treatment (Spearman r > 0.67, *P*<0.005) and 35 genes showed a strong negative correlation with survival (Spearman r > -0.63, *P*<0.005). Based on these correlated genes, an AsiSS was created. In the BRCA cohort the top 25% AsiDNA sensitivity scoring patients were identified, and DNA repair gene expression levels of these patients were rank ordered and sorted according to AsiSS. The top 7 genes with significantly lower expression in the 25% top AsiDNA sensitive patient group were retrieved (XRCC2, MRE11A, POLQ, BRCA2, NBN, FANCA, RAD54B; 10^{-14} < p value < 10^{-9}). To validate the predictive value of these genes, cell lines from the CCLE were rank ordered according to the AsiSS, and response to AsiDNA of 20 cell lines (10 predicted sensitive; 10 predicted resistant) as well as the expression level of the top 7 genes were analyzed. Importantly, cells predicted resistant showed significantly higher survival (mean survival = 80%) compared to cells predicted sensitive (mean survival = 40%; p < 0.01). Among the 7 retrieved genes, gene expression analysis revealed a correlation between sensitivity to AsiDNA and the expression of BRCA2 (Pearson r: 0.75), NBN (r: 0.62), MRE11A (r: 0.6), RAD54B (r: 0.54), FANCA (r: 0.6) and XRCC2 (r: 0.55) genes (0.001< p <0.05). This set of genes could be used to stratify patients for future clinical trials involving AsiDNA.

Conclusion: Overall, our results highlight the interest of retrospective analysis based on patient databases to retrieve gene biomarkers predictive of drug outcome. As AsiDNA is being currently tested in a clinical trial, a potential exists for a rapid validation of our gene set in the aim to develop a Biomarker-driven patient selection strategy for AsiDNA treatment.

Introduction

Multiple DNA Repair pathways inhibition by AsiDNA

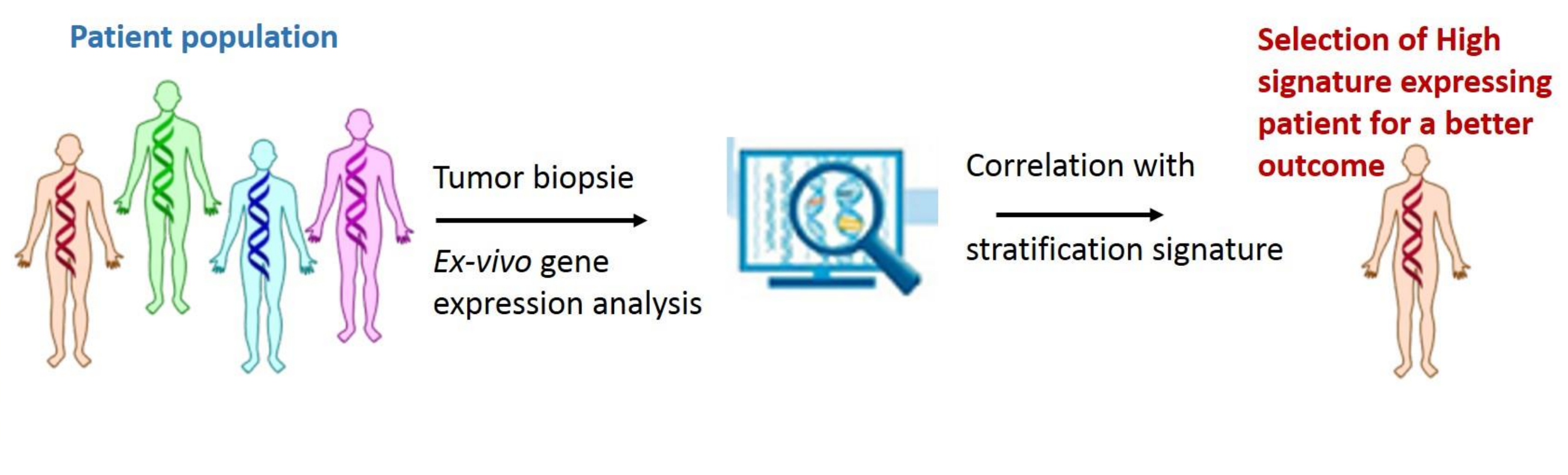
Dbait are short and stabilized DNA molecules that mimic DSBs. AsiDNA, a molecule of Dbait family, acts by hijacking and hyper-activating the DNA-dependent protein kinase (DNA-PK), and Poly(ADP-Ribose) Polymerase (PARP), which modify the chromatin and consequently inhibit the recruitment at the damage sites of many proteins involved in the DSB (HR and NHEJ) repair pathways. This strategy sensitizes tumors to DNA damaging therapies such as radiotherapy and chemotherapy.



Advantage of a patient selection strategy

Patient selection for early phase oncology trials is of utmost importance because of the cascading effects it has on subsequent drug development and a drug's ultimate success as a safe, beneficial and cost-effective treatment.

Selecting patients based on different gene expression profile has the advantage of limiting tumor resistance, as observed in tumors selected based on one gene alteration.



Patients whose tumors show a high stratification signature would benefit from AsiDNA treatment

Development of a pan-tumor AsiDNA sensitivity signature

Wide AsiDNA Sensitivity Signature from Breast cancer cell lines

First, we performed correlation analysis between sensitivity to AsiDNA and transcriptomes of 12 breast cancer cell lines[1].

1. Basal gene expression analysis of 12 breast cancer cell lines

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2. Analysis of survival to AsiDNA treatment

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3. Correlation between gene expression and survival

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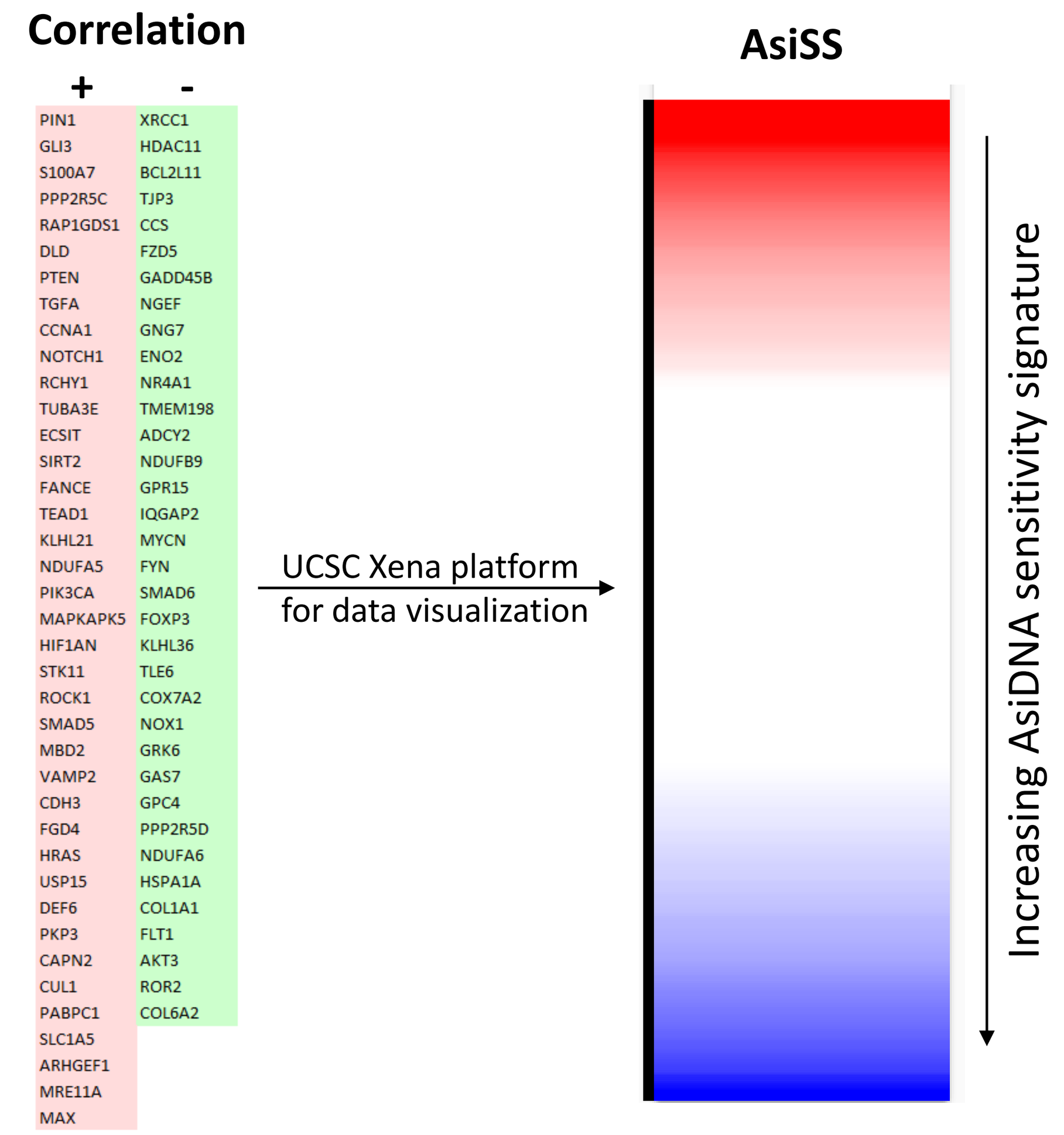
39 profiles positively correlated genes (Spearman r > 0.67, *P*<0.005)
35 negatively correlated genes (Spearman r > -0.63, *P*<0.005)



Identification of the most predictive genes of sensitivity to AsiDNA independently of tumor types

1. Patients from the breast cancer (BRCA) cohort were sorted according to the AsiDNA signature -The bottom AsiDNA sensitivity scoring patients were identified.

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2. Genes involved in DNA repair whose expression was negatively correlated with AsiDNA sensitivity were rank ordered.

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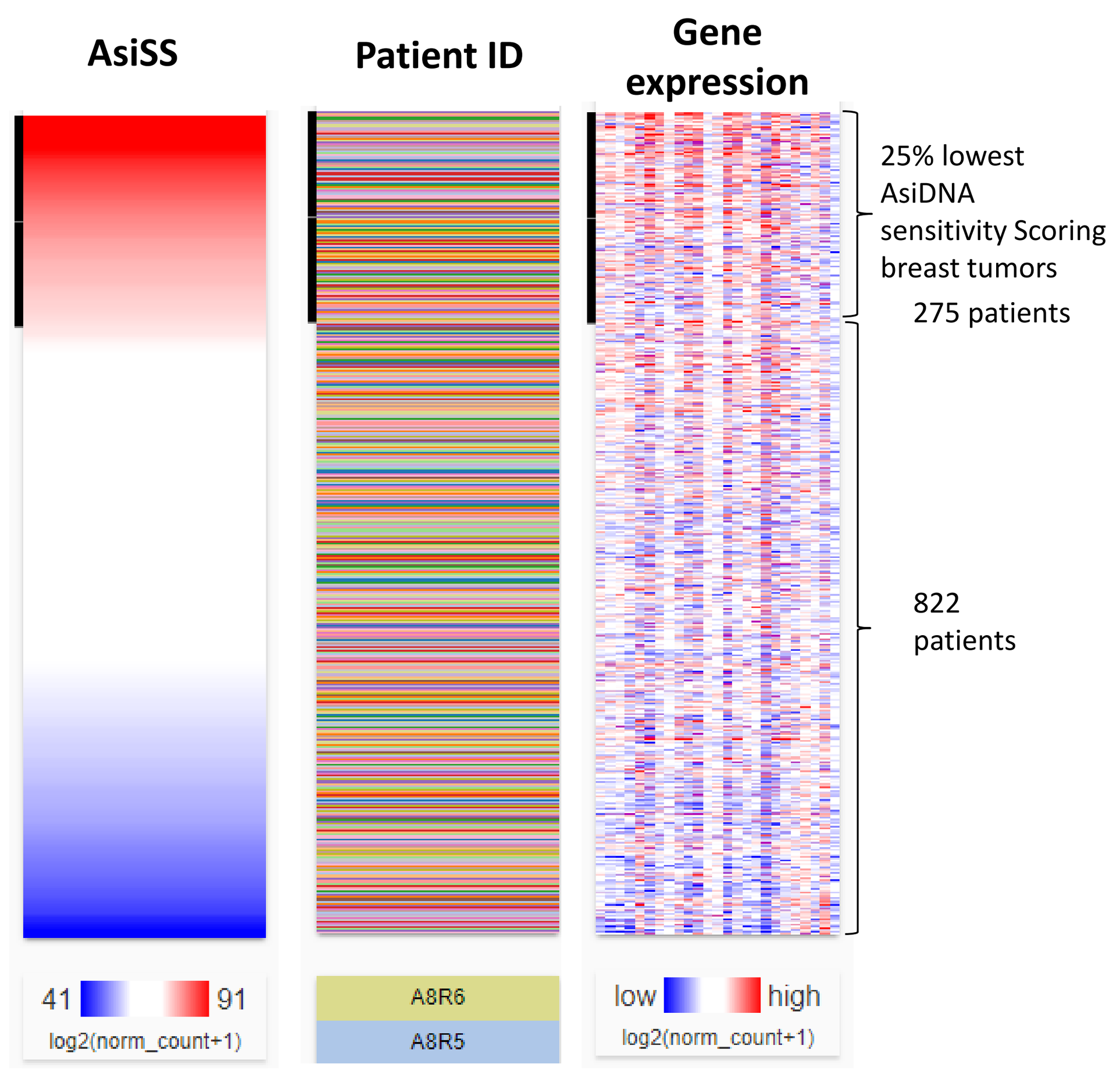
3. Genes with significantly higher expression in the bottom 25% AsiDNA sensitivity group compared to the rest were identified with t and P values (Welch's T test):



XRCC2; MRE11A; POLQ; BRCA2; NBN; FANCA; RAD54B

Patient stratification signature: Bench validation

Prediction of sensitivity to AsiDNA of cell lines from the Cancer Cell Line Encyclopedia (CCLE)

The AsiDNA sensitivity signature has been used to rank order 973 cell lines of the CCLE database

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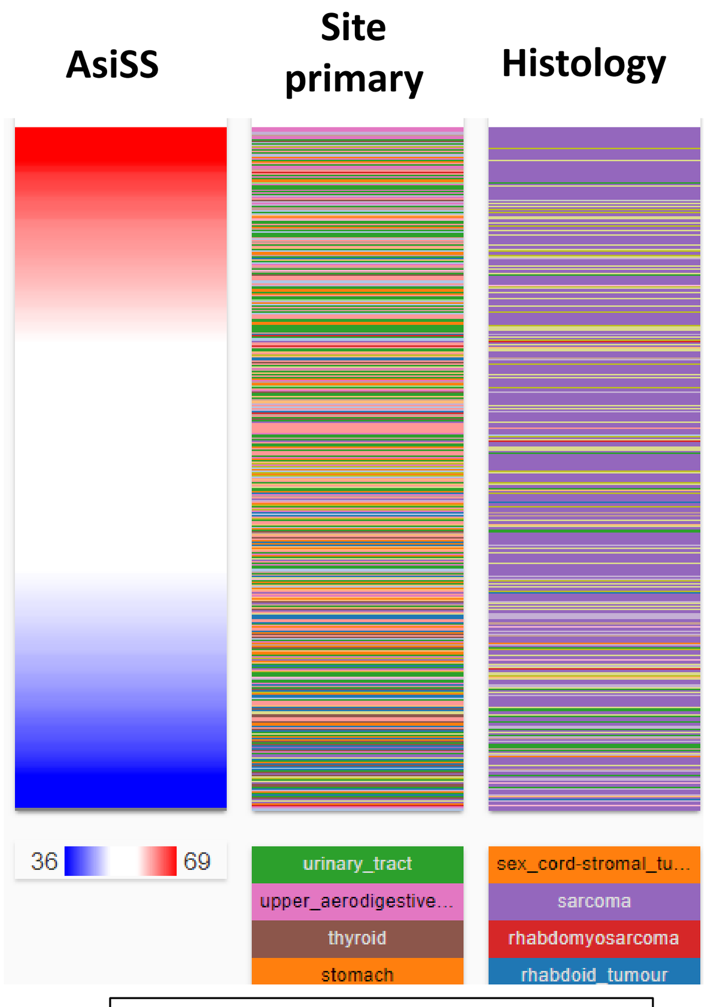
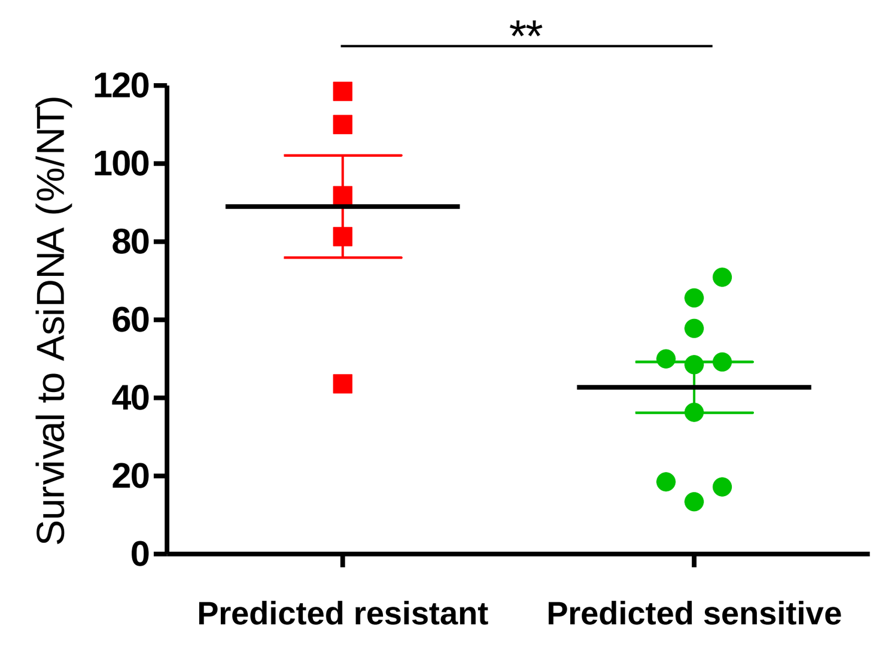
Selection of cells that would be **sensitive (High AsiSS)** or **resistant (Low AsiSS)** to AsiDNA from our Lab cell library

Analysis of sensitivity to AsiDNA | Gene expression analysis (RTqPCR)



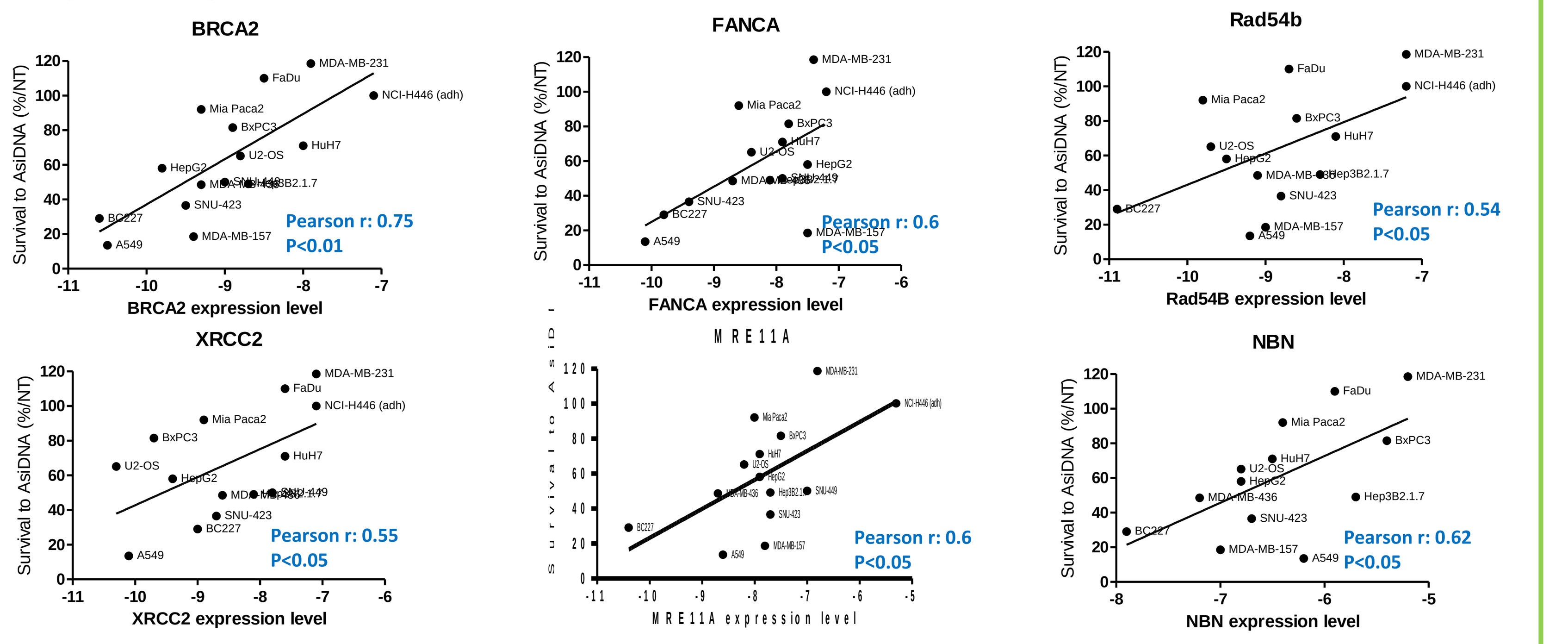
No clear dominant primary site for AsiDNA sensitivity scores

1. Sensitivity to AsiDNA



Cells predicted resistant showed significantly higher survival (mean survival = 80%) compared to cells predicted sensitive (mean survival = 40%; p < 0.01)

2. Signature genes expression analysis and correlation with survival



Positive correlation between 6 genes (among the 7 identified) and survival to AsiDNA
→ This set of genes could be used to stratify patients for future clinical trials involving AsiDNA

Conclusion: Overall, our results highlight the interest of retrospective analysis based on patient databases to retrieve gene biomarkers predictive of drug outcome. As AsiDNA is being currently tested in a clinical trial, a potential exists for a rapid validation of our gene set in the aim to develop a Biomarker-driven patient selection strategy for AsiDNA treatment

Related publications:

- C. Le Tourneau, et al. (2016*) Br J Cancer. May 3. doi: 10.1038/bjc.2016.120.* First-in-human phase I study of the DNA repair inhibitor DT01 in combination with radiotherapy in patients with skin metastases from melanoma.
- M. Quanz, et al. (2009) *PloS ONE* 4(7) e6398. Hyperactivation of DNA-PK by Double-Strand Break Mimicking Molecules Disorganizes DNA Damage Response.
- Jdey W, Thierry S, Russo C, Devun F, Al Abo M, Noguiez-Hellin P, et al. Drug-Driven Synthetic Lethality: Bypassing Tumor Cell Genetics with a Combination of AsiDNA and PARP Inhibitors. Clin Cancer Res. 2017 Feb 15;23(4):1001–11.
- Jdey W, Thierry S, Popova T, Stern M-H, Dutreix M. Micronuclei frequency in tumors is a predictive biomarker for genetic instability and sensitivity to the DNA repair inhibitor AsiDNA. Cancer Res. 2017 Jun 6;canres.2693.2016.

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