A Biomarker that can predict which indication will be approved by the FDA

by Steen Knudsen, Anker Hansen, Thomas Jensen, Jon Askaa and Peter Buhl Jensen

Medical Prognosis Institute, Venlighedsvej 1, 2970 Hørsholm, Denmark.

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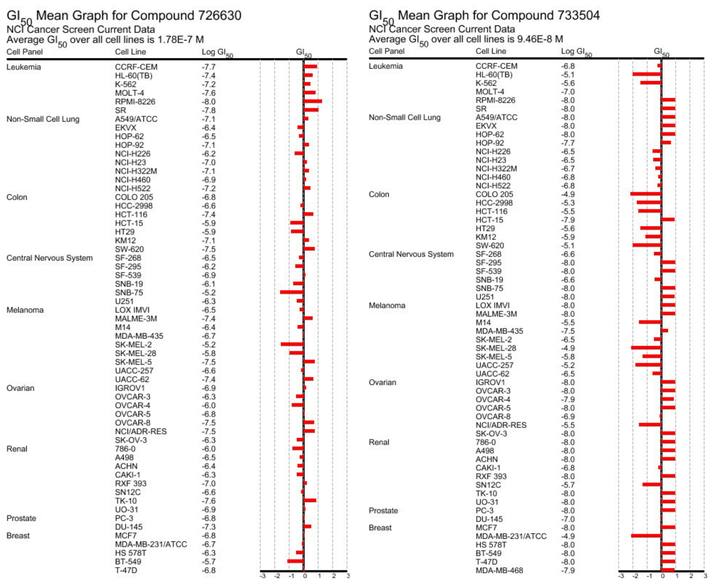
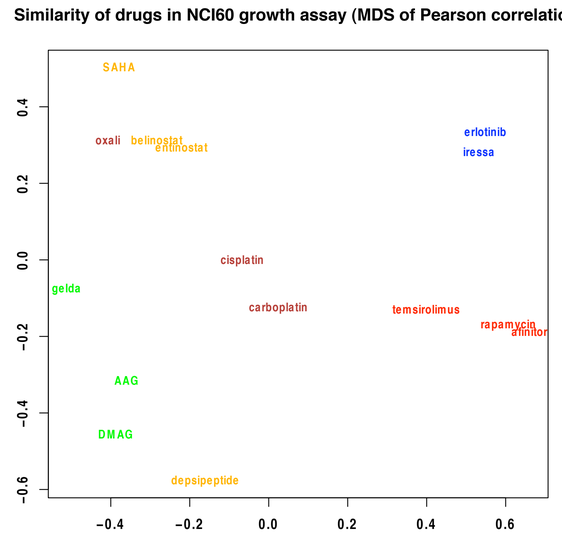
1. Cancer cell lines show differential sensitivity to cancer drugs

Belinostat (HDAC inhibitor) **Afinitor (mTOR inhibitor)**



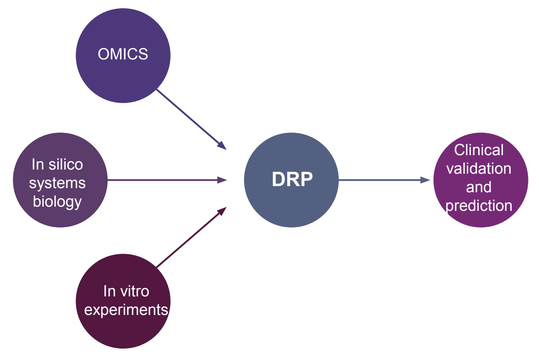
NCI60 profiling.
NCI has tested a large number of drugs for their ability to inhibit growth (GI50) of cancer cell lines. The red bars show deviation from average growth inibition for a given drug. Shown are the GI50 vectors for Belinostat and Afinitor. They differ a lot.

2. Sensitivity pattern is related to drug mode of action



Drug similarities
If the growth inhibition vectors (as shown in red in panel 1) are used to calculate distances between drugs, it turns out that drugs with similar modes of action group together.

3. Explanatory model based on gene expression



Drug Response Predictor (DRP)
If a growth inhibition vector (as shown in red in panel 1) is combined with baseline transcriptomics and systems biology, a model results that can predict a patient's clinical response to the drug based on a pre-treatment biopsy.

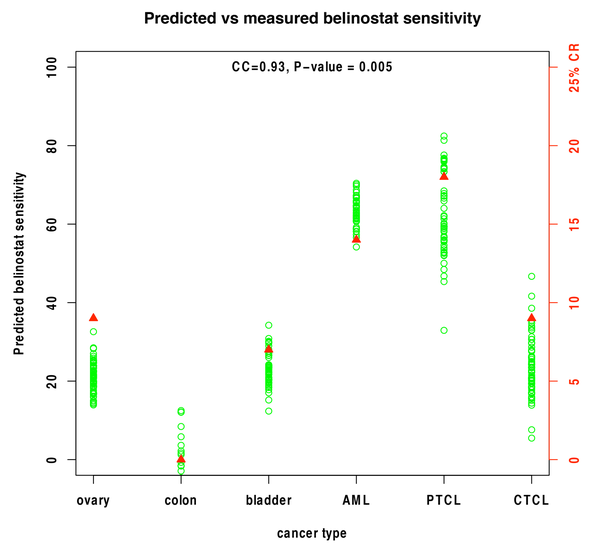
4. Summary of 24 clinical validation trials: 20 positive

Cancer	Patients	Drug(s)	Patent	Primary (sec) endpoint	P value	ORR	ORR Bottom 10%	ORR Top 10%
Breast	268	tamoxifen	Issued	RFS	0.03*			
Breast	136	tamoxifen	Issued	DMFS	0.03*			
Breast	102	16 combinations	Issued	DMFS	0.006*			
DLBCL	166	CHOP	Issued	CR (OS)	0.007*			
DLBCL	414	(R)-CHOP	Issued	OS	1e-15*			
Breast	244	11 combinations	Issued	pCR	8e-12*	20%	8%	32%
Breast	125	TET/FEC	Issued	pCR	0.007*	44%	31%	62%
Breast	24	docetaxel	Issued	pCR	0.02*	46%	0%	100%
DLBCL (miRNA)	116	R-CHOP/CHOEP	Issued	CR	0.03*	89%	82%	100%
Hodgkin	130	ABVD	Issued	CR	0.003*	71%	62%	92%
AML	13	Belinostat+idarub.	Issued	ORR	0.02*	40%	0%	100%
AML	88	7 combinations	Issued	CR	0.02*			
Breast	44	Oncology Drug X	Pending	CR	0.01*	55%	0%	100%
NSCLC	21	Tarceva (erlotinib)	Pending	PFS	0.02*			
NSCLC	50	cisplatin	Issued	OS	0.03*			
Breast	24	cisplatin	Issued	Miller-Payne	0.02*	63%	67%	100%
Ovarian	28	cisplatin	Issued	OS	**0.06**			
Breast	114	epirubicin	Pending	pCR (DMFS)	**0.9 (0.03)**	14%	8%	25%
AML	53	decitabine	Issued	ORR	0.01*	50%	25%	75%
Breast	19	Anastrozole	Pending	ORR	**0.9**			
AML	79	HAM	Issued	CR	**0.45**			
Myeloma	84	VAD	Issued	CR	0.004*	95%	~50%	100%
ALL	161	Methotrexate	Issued	WBC count	0.008*			
Myeloma	169	bortezomib	Issued	ORR	0.008*	50%	23%	29%

Meta-analysis of 24 clinical trials using Fisher's combined probability test yields a p-value of 1e-35.

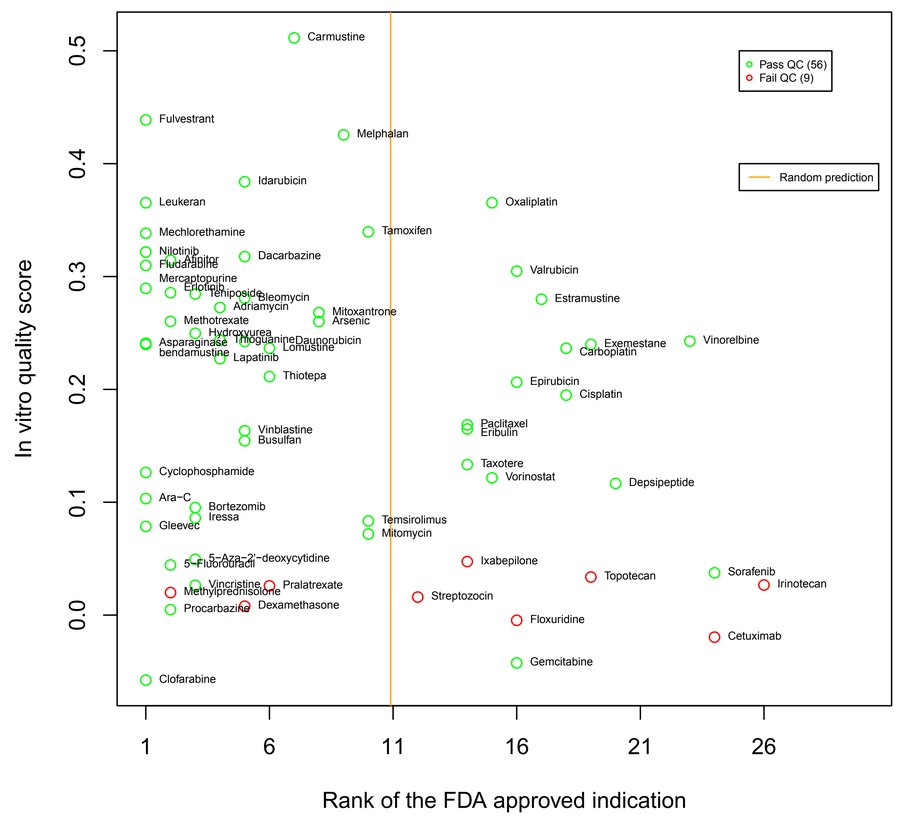
Stouffer's Z-score weighed by number of patients in each study gives a p-value of 2e-36.

5. Explanatory model can predict cancer type with highest response rate



Predicting response rates
Observed differences in predicted sensitivity to a drug (belinostat, green circles), correlate with differences in observed response rates from clinical trials (red triangles, left axis).
This study was repeated with 3 other drugs: decitabine, vorinostat and sorafenib and similar correlations were observed in all three cases.

6. Explanatory model can predict which indication will be approved by the FDA



Rank of the FDA approved indication for 65 cancer drugs. For each drug, a biomarker was developed and used to predict the relative sensitivity of 27 cancer indications to the drug. The figure shows the rank of the indication approved by the FDA for all 65 drugs. Where more than one indication has been approved, the highest rank is shown. In vitro data for nine drugs (14%) failed quality criteria (red circles). Among the remaining, the approved indication was correctly predicted for 12 drugs (21%, P=0.0005). The approved indication was among the top 5 predictions for 32 drugs (57%, P=0.002). A random prediction would on average rank at 10.9 (orange line). 73% of the predictions (green circles) were better than random. While there is an overweight of drugs approved for leukemia and lymphoma on the left, and an overweight of drugs approved only for solid tumors on the right, simply predicting hematological cancers to be most sensitive would fare no better than random prediction (orange line).

7. Future perspectives

MPI has developed biomarkers for six anticancer drugs currently in the pipeline at biopharmaceutical companies, allowing for a future prospective test of their ability to predict an indication that will later be approved by the FDA (although a development bias cannot be ruled out).

8. References

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3. Pieter Sonneveld, Mark Vanduin, Steen Knudsen, et al. A novel chemosensitivity index for chemotherapy correlates to myeloma cell lines resistance and patients refractoriness. Presented at XXII International Myeloma Workshop in Washington, DC, Feb 26, 2009

4. Junjie Chen, Steen Knudsen, Wiktor Mazin, Jesper Dahlgaard, and Baolin Zhang. A 71-gene signature of TRAIL sensitivity in cancer cells. (October 25, 2011); Mol Cancer Ther, 10.1158/1535-7163.

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Contact info: Steen Knudsen, steen@medical-prognosis.com