A clinical trial of cResponse, a functional assay for cancer precision medicine

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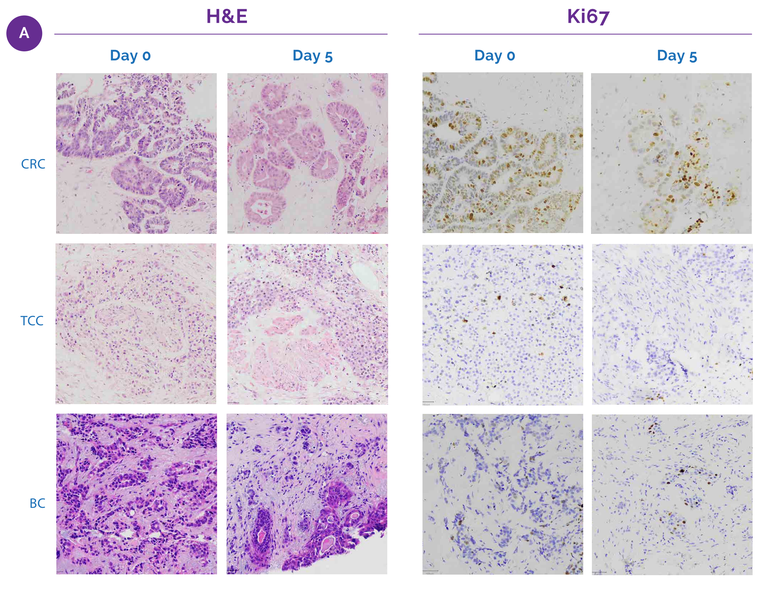
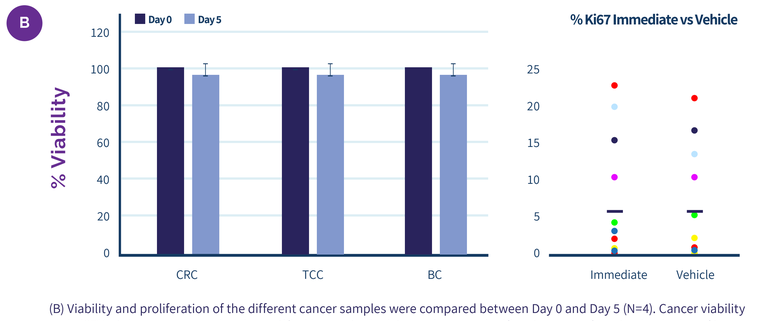
Abstract

Precision cancer therapy has the potential to revolutionize treatment and improve outcome. While genomic analysis has become central to cancer personalized medicine, recent studies have not shown that it drastically improves the patient's survival as compared to drug selection. Additionally, the presence of genomic mutations may suggest several treatment options without elucidating which of the drugs or combination of drugs might yield superior clinical response. Moreover, for many drugs no genetic predictive biomarkers are available. To advance cancer precision diagnostics, we have developed cResponse, a functional drug sensitivity platform to determine individualized patient treatment regimens. Fresh patient cancer tissue samples are obtained by biopsy or resection and sectioned to 300 uM slices which when cultured in the cResponse platform, retain their architectural character and proliferative capacity. We show that cResponse preserves human cancer tissue together with its microenvironment, including endothelial and immune cells, at a high viability (>90%) with continued cell division for 7 days in over twenty types and sub-types of solids tumors. We utilize this extended period of viability to (a) perform rapid genomic profiling to help prioritize drugs to be tested by cResponse and (b) evaluate the effects of slow-acting drugs such as targeted therapy. To test the accuracy of the cResponse assay to predict patient response to cancer treatment, we first conducted a comparative study on thirty-seven patients with metastatic pancreatic cancer receiving platinum-based drugs and Olaparib. The tissues were treated for 5 days ex vivo and assessed with histological staining. Tissues were assigned a viability score (ranging from 0 to 100) based on an algorithm composed of a panel of immunohistochemical markers. Clinical correlation showed a specificity of 90% and a sensitivity of 88%. Subsequently, we performed a clinical study on biopsies from twenty-eight patients with different cancer types receiving diverse chemotherapeutic and targeted agents. Cancer types included bladder, pancreatic, lung, colorectal, breast and sarcoma. The cResponse score was compared to the clinical response and showed that cResponse could predict the patient's response with a specificity of 78% (7/9) and a sensitivity of 95% (18/19). **Taken together, a total of 65 samples demonstrated a specificity of 87% (33/38) and a sensitivity of 96% (25/27).** In the future, the integration of this platform in the clinical setting, to help direct drug choices for anti-cancer treatment may lead to improved patient outcomes.

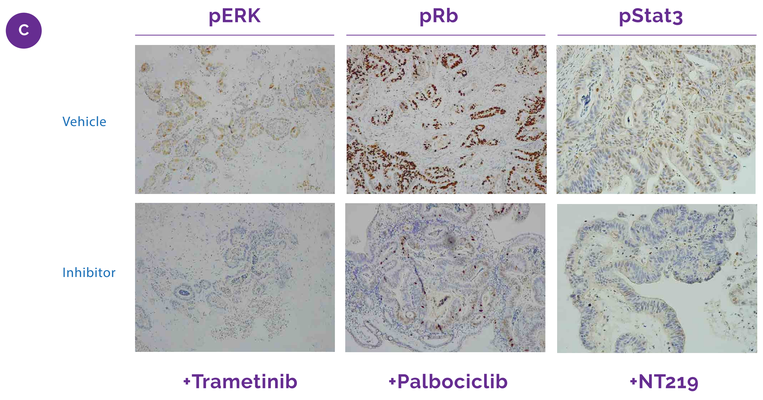
cResponse Ex Vivo Organ Culture System Preserves the Tumor Microenvironment



(A) Resectioned Colorectal Cancer (CRC), Transitional Cell Carcinoma (TCC) and Breast Cancer (BC) were cultured in an ex vivo organ culture assay capable of preserving the tumor microenvironment. Representative images of the tissues are compared on Day 0 when the tissue was received and after 5 days of culture. H&E and Ki67 stains are shown.

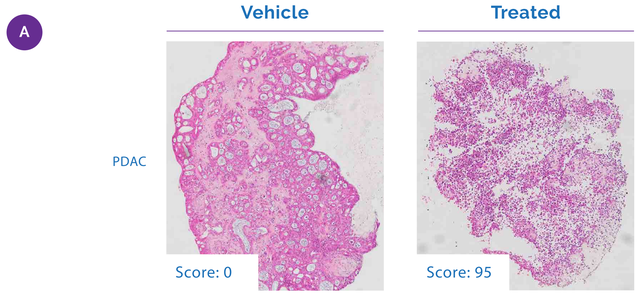


(B) Viability and proliferation of the different cancer samples were compared between Day 0 and Day 5 (N=4). Cancer viability and ki67% stain were assessed and quantified by a pathologist showing non-significant changes from the beginning of the assay.



(C) The effectivity of targeted drug treatments to modulate their targets in ex vivo culture was assessed after 24 hours. Tissues were treated with either Trametinib, a pERK inhibitor, Palbociclib, a CDK4/6 inhibitor or NT219, a pStat3/IRS inhibitor as indicated. Their respective molecular targets were evaluated by IHC staining.

Comparative Study



(A) A comparative study was conducted using cResponse to predict the clinical response of patients with metastatic pancreatic cancer. Tumor section from PDAC PDX models were assessed by cResponse and correlated to the original patient's clinical response to platinum and PARPi at the time of PDX generation. Re presentative images are shown of a tissue sample after 5 days in cResponse with vehicle and cisplatin.

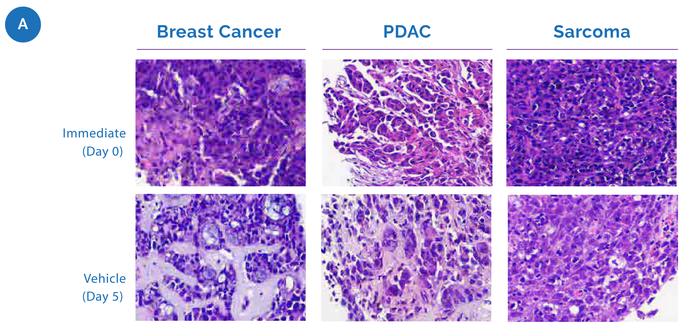
B

cResponse score was compared to the clinical response for 37 samples showing: 90% specificity (26/29) and 88% sensitivity (7/8)

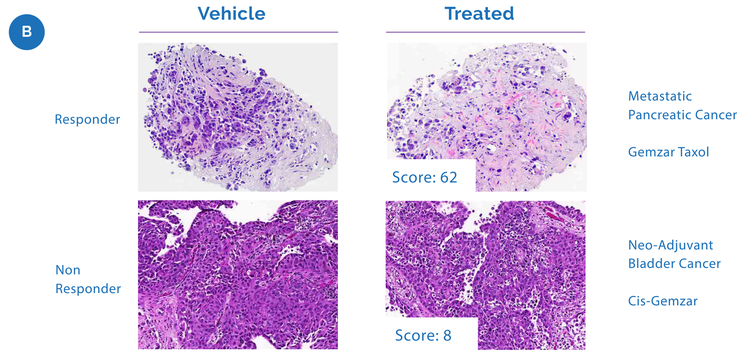
	Patient	Score	Clinical Response	Treatment
0-66 : No Response	126b	0	No-Response	Olaparib
	217b	0	No-Response	Olaparib
	321a	4.5	No-Response	Cisplatin
	187b	7	No-Response	Olaparib
	126a	8.5	No-Response	Cisplatin
	187a	9	No-Response	Cisplatin
	418a	14	No-Response	Cisplatin
	185b	16	No-Response	Olaparib
	291a	21.5	No-Response	Cisplatin
	291b	22.9	No-Response	Olaparib
	227b	24	No-Response	Olaparib
	194a	24	No-Response	Cisplatin
	210a	24.7	No-Response	Cisplatin
	143b	26.7	No-Response	Olaparib
	375a	29	No-Response	Cisplatin
	185a	32	No-Response	Cisplatin
	421a	32	No-Response	Cisplatin
	210b	33.7	No-Response	Olaparib
	421b	37	No-Response	Olaparib
	265a	49	No-Response	Cisplatin
	265b	49.1	No-Response	Olaparib
	143a	53.7	No-Response	Cisplatin
	217a	61	No-Response	Cisplatin
	145b	61.1	No-Response	Olaparib
	96%	63.8	Response	Olaparib
	135a	66	No-Response	Cisplatin
	228a	66	No-Response	Cisplatin
	145a	66.5	Response	Cisplatin
66-100 : Response	326a	69	Response	Cisplatin
	259a	69	Response	Cisplatin
	228b	74	Non-Response	Olaparib
	203a	76	Response	Cisplatin
	203b	82	Response	Olaparib
	123a	87	Response	Cisplatin
	87a	87	No-Response	Olaparib
	324a	90	Non-Response	Cisplatin
	467a	100	Response	Cisplatin

(B) Summary of cResponse score compared to the clinical response based on oncologist evaluation (sensitive - SD, PR, CR; resistance - PD). Patients received platinum-based therapy followed by PARPi. Response to each treatment was recorded independently. cResponse score was assessed on PDX tumor chunks recapitulating the specific clinical scenario and response to platinum and PARPi.

Clinical Study



(A) Biopsies from breast cancer (BC), pancreatic cancer (PDAC) and sarcoma were obtained prior to initiation of patient treatment and maintained in the ex vivo organ culture for 5 days. Representative images are shown of each cancer type at Day 0 and Day 5 showing high viability and preservation during the culture assay.



(B) Representative images of samples from the clinical trial which were responders and non-responders. The responder is from a pancreatic cancer patient treated with Gemzar-Taxol, while the non-responder is from a bladder cancer patient treated with Cisplatin and Gemzar.

C

cResponse score was compared to the clinical response for 28 samples showing: 78% specificity (7/9) and 95% sensitivity (18/19)

	Patient	Score	Clinical Response	Tissue Type	Treatment
0-40 Progressive Disease	e132	0	PD	Bladder	Cis-Gemzar
	55	8	PD	Bladder	Cis-Gemzar
	25	8	PD	Bladder	Cis-Gemzar
	p55	13	PD	Sarcoma	Pazopanib-Everolimus
	c229	13	PD	Esophageal	Paclitaxol
	70	17	PD	Bladder	Cis-Gemzar
	c150	31	PR	CRC	Folfox-Cetuximab
	E93	37	PD	Pancreatic	FOLFIRNOX
40-80 Stable Disease & Partial Response	C139	45	SD	Bladder	Cis-Gemzar
	159	46	SD	Sarcoma	Ifosamide-Etoposide
	c161	50	SD	Pancreatic	FOLFIRNOX
	117	62	SD	Pancreatic	FOLFIRNOX
	156	64	PR	Pancreatic	Gemzar-Taxol
	107	66	SD	Pancreatic	FOLFIRNOX
	130	74	PD	Bladder	Cis-Gemzar
	c83	75	PR	Bladder	Cis-Gemzar
80-100 Partial Response & Complete Response	170	82	PD	Unknown	Cis-Gemzar
	41	86	PR	Bladder	Cis-Gemzar
	149	86	PR	CRC	FOLFOX
	C168	90	PR	Pancreatic	FOLFIRNOX
	115	91	PR	Pancreatic	FOLFIRNOX
	128	100	PR	Bladder	Cis-Gemzar
	190	92	PR	Bladder	Cis-Gemzar
	33	100	PR	Bladder	Cis-Gemzar
	63	100	PR	Bladder	Cis-Gemzar
	95	100	PR	Bladder	Cis-Gemzar
	105	100	PR	Bladder	Cis-Gemzar
	c135	100	CR	Breast	AC-TC

(C) Table of the results from the cResponse test and clinical correlation, leading to overall sensitivity and specificity calculations. Thresholds for response were 0-40 for progressive disease, 40-80 for stable disease & partial response and 80-100 for partial response and complete response. Clinical response was determined by either pathological response or clinical imaging.

Conclusions

- cResponse assay maintains high viability of the resected human cancer tissue, preserving the 3D architecture together with its microenvironment, including endothelial and immune cells for 5 days.
- Cell signaling pathways within the cancer tissue are maintained as demonstrated by the downregulation of target proteins after treatment ex vivo.
- Similar to resected tissue, we show the ability to preserve core biopsies at high viability in our system and evaluate their response to drugs.
- In a comparative study in pancreatic metastatic cancer, the cResponse score was compared to the clinical response for 37 samples, showing 90% specificity and 88% sensitivity.
- An expanded clinical study was performed on biopsies from patients with locally advanced and metastatic cancer in patients receiving diverse chemotherapeutic and targeted anti-cancer agents. Cancer types included bladder, pancreatic, lung, colorectal, breast and sarcoma. In 28 biopsy samples, the cResponse assay demonstrated 78% specificity and 95% sensitivity when cResponse assay as compared to clinical outcome.
- **Overall, in 65 patients, cResponse demonstrated a specificity of 87% (33/38) and a sensitivity of 96% (25/27) as compared to clinical outcome.**

A total of 65 samples demonstrates specificity of 87% (33/38) and sensitivity of 96% (25/27)

References

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