Abstract #1147

ENHANCED CCNG1 EXPRESSION IN TUMORS MAY PREDICT CLINICAL BENEFIT FROM DELTAREX-G, A TUMOR TARGETED RETROVECTOR ENCODING A CCNG1 INHIBITOR GENE

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Abstract

Background: Metastatic cancer is associated with an invariably fatal outcome. Therefore, innovative therapies are urgently needed. Although expanded access for DeltaRex-G, a tumor targeted retrovector encoding a CCNG1 inhibitor gene, is ongoing for an intermediate-size (n=up to 40) population of advanced sarcoma and pancreatic cancer, more data is needed to identify patients who are likely to benefit from DeltaRex-G gene therapy. In this study, we retrospectively analyzed CCNG1 expression in archived tumors of patients who were previously treated with DeltaRex-G and who are active candidates for DeltaRex-G therapy.

Methods: Archived formalin-fixed paraffin-embedded (FFPE) tumor specimens (n=58) from patients with solid malignancies who are actively followed at the Cancer Center of Southern California were collected, processed, and subjected to RNA sequencing. Briefly, RNA-seq libraries were sequenced to generate 50 million reads that were aligned using Kallisto v0.42.4 to GENCODE v23 transcripts with default parameters. Only protein-coding, IGH/K/L-, and TCR-related transcripts were retained for downstream processing, resulting in 20,062 protein-coding genes. Gene expression was quantified as transcripts per million (TPM) and log2-transformed. A gene expression level is presented as low, medium or high depending on the expression level of a such gene in patients of the reference cohort. Low = <17%; Medium = 17%-83%; High = >83%.

Results: Thirty-two male and 26 female subjects, ages ranging from 16 to 86 years were studied. Forty-nine (84.4%) patients had sarcoma, 3 (5.2%) had urothelial carcinoma,2 (3.5%) had breast carcinoma, 2 (3.5%) had pancreatic cancer, 1 (1.7%) had Sertoli cell tumor, 1 (1.7%) had adenocarcinoma of appendix. Eleven (19%) tumors showed high CCNG1 expression, 44 (76%) tumors had medium expression, and 3 (5.2%) tumors had low CCNG1 expression. Of note, in DeltaRex-G treated patients, the tumor of one 14-year survivor with metastatic pancreatic adenocarcinoma in sustained remission had 24 % CCNG1 expression, one 3-year survivor with metastatic chondrosarcoma metastatic to lung with stable disease had 74% CCNG1 expression, one 2-year survivor with early stage HR+ HER2+ breast cancer in remission had 23% CCNG1 expression, and one 2-year survivor with early stage triple negative breast cancer in remission had 74% CCNG1 expression.

Conclusion: Taken together, these data indicate that (1) Medium to high CCNG1 expression was found in 95% of tumors studied, (2) Patients with medium CCNG1 expression who received DeltaRex-G had clinical benefit and are alive in sustained remission or with stable disease 2-14 years from DeltaRex-G treatment initiation, and (3) Prospective studies are warranted to correlate CCNG1 expression level and response to DeltaRex-G therapy.

Mechanism of action

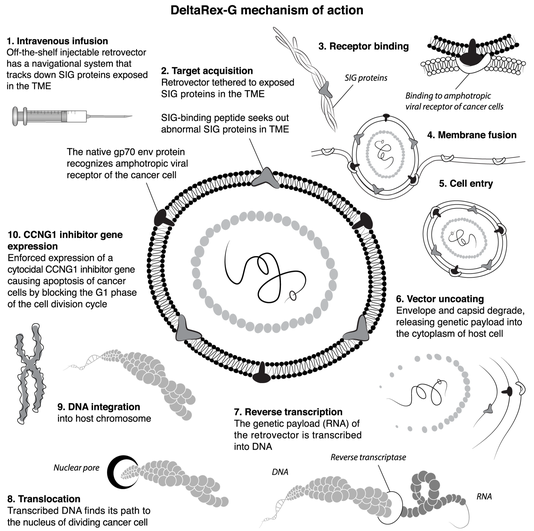

Figure 1 Legend: Ten-step illustration of DeltaRex-G mechanism of action
The DeltaRex-G nanoparticle displays a SIG-binding peptide derived from coagulation vWF on its gp70 envelope protein. When injected i.v., DeltaRex-G seeks out the tumors and accumulates in cancerous lesions by binding to abnormal SIG proteins exposed in the TME as a result of tumor invasion. This chimeric retrovector has the innate property of binding to the natural amphotropic viral/cell receptor, fusing, entering, uncoating and integrating randomly into the chromosomes of only actively dividing cells (i.e., cancer cells, stroma producing tumor associated fibroblasts and tumor microvasculature), sparing normal cells. DeltaRex-G bears a cytocidal CCNG1 inhibitor gene, which causes cell death through apoptosis.
CCNG1 (cyclin G1); SIG (signature), vWF (von Willebrand factor), TME (tumor microenvironment).

Results

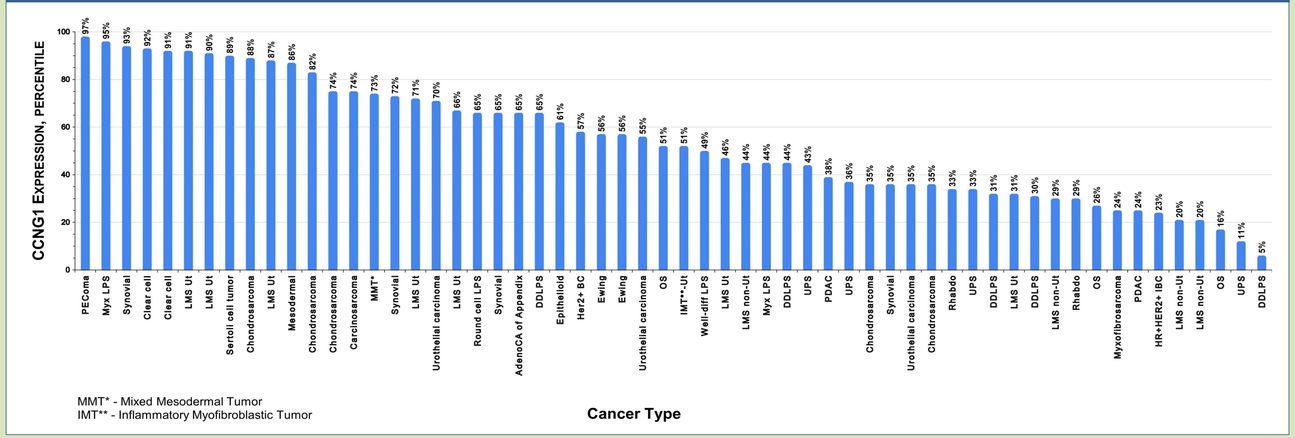

Figure 2 Legend: Waterfall plot of CCNG1 expression level in cancer. Low = <17%; Medium = 17%-83%; High = >83%

Case Report and Oncogenic Mechanisms Activating CCNG1

A 75-year-old woman with HR+ HER2+ and 23% CCNG1+ early- stage invasive breast cancer was treated with adjuvant DeltaRex-G, Letrozole and Trastuzumab instead of chemotherapy.

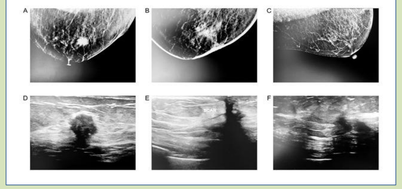

Figure 3 Legend:
A, B, C: Mammogram at diagnosis, 6 months, and 1 year after treatment initiation
D, E, F: Ultrasound at diagnosis, 6 months, and 1 year after treatment initiation. No recurrence of breast cancer was identified at 6 months, 1 year and 2 years after diagnosis.

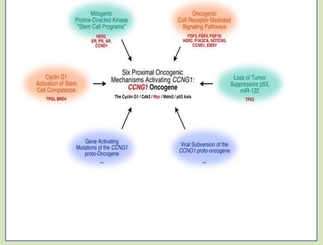

Figure 4 Legend: Six proximal oncogenic mechanisms activating the CCNG1 oncogene. The oncogenic drivers amplified in this case study are marked RED.0

Conclusions

Taken together, these data indicate that

- ✓ Medium to high CCNG1 expression was found in 95% of tumors studied
- ✓ Patients with medium CCNG1 expression who received DeltaRex-G had clinical benefit and are alive in sustained remission or with stable disease 2-14 years from DeltaRex-G treatment initiation
- ✓ Prospective studies are warranted to correlate CCNG1 expression level and response to DeltaRex-G therapy

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