**STUDY OBJECTIVE**

To determine the expression levels of HER3, the target of the investigational ADC U3-1402, in solid tumors and normal tissues.

**METHODS**

- We characterized a pan-cancer tissue microarray (TMA) set (established at Pathology, Basel University Hospital, and supported by Daiichi Sankyo, Inc.)
- **TMA**
  - Comprised of 2376 samples including 17 solid cancer types and 25 normal tissues (Figure 1) and supported by Daiichi Sankyo, Inc.
- Higher scores for genes regulating the cell cycle in cancer tissues than in normal tissues
- **Richness of cancer-associated fibroblasts (CAF) in pancreatic adenocarcinoma (PAAD)**
- **Broad Institute Cancer Cell Line Encyclopedia (CCLE)**
- **RNAseq** (log₂ [RPKM + 1])
- **TCGA** (R = 0.472)
- **CCLE (R = 0.823)**
- **Experiment design**
  - HER3 expression levels showed a consistent and positive correlation with expression of CDH1, an epithelial marker, and supported by Daiichi Sankyo, Inc.

**RESULTS**

- Enriched genes showed a consistent and positive correlation with expression of CDH1, an epithelial marker, in all 2 data sets (Figure 5).
- There was an overall correlation between EdgeSeq HER3 mRNA data and IHC for HER3 protein (Figure 6).

**CONCLUSIONS**

- HER3 expression was confirmed in tumor and highly expressed on the membrane in multiple tumor types, including melanoma, breast, colorectal, prostate, and bladder cancers, as well as intestinal gastric and ovarian cancer subtypes.
- The regulation of HER3 expression was shown to be highly complex.
- Cell cycle regulation and HER3 level regulation were observed, plus additional cell type-specific regulations.
- Although high correlations between RNA and HER3 protein levels were observed in some cancer types.
- The unique protein levels HER3 regulation observed in tumor cells warrants further investigation into the significance of HER3 expression levels in the context of HER3 signaling.
- Further fine-tuned investigations and future animal research in this area will help to reframe clinical trial strategies.

**REFERENCES**


**ACKNOWLEDGMENTS**

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**BACKGROUND**

- Antibody drug conjugates (ADCs) have recently emerged as a targeted therapy for solid tumors.
- HER3 is an evolutionarily conserved protein tyrosine kinase and a key regulator in pathways associated with cell survival and proliferation.
- HER2, a member of the human epidermal growth factor receptor (HER) family, is overexpressed in many breast cancers.
- The HER3 ligand is GGF in mice, and EGF and neuregulin (NRG) in humans and may recognize more than one receptor tyrosine kinase (RTK), and overexpression has been associated with worse clinical outcomes.
- There are currently approved HER2-directed agents.
- HER3 is a novel, investigational next-generation ADC composed of the fully human monoclonal antibody U3-1402 and a novel, lipophilic maytansinoid payload.
- HER3 is being evaluated for the treatment of cancers that express HER3, including breast cancer, NSCLC, colon cancer, prostate cancer, and others.

**Table 1. Gene Signature Analysis of TMA EdgeSeq and TCGA RNAseq Data, Continuum**

<table>
<thead>
<tr>
<th>RNAseq TMA</th>
<th>HER3 mRNA expression pattern (Pathway)</th>
<th>Higher scores for genes regulating the cell cycle in cancer tissues than in normal tissues</th>
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<tr>
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<td>Higher scores for genes regulating the cell cycle in cancer tissues than in normal tissues</td>
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**Figure 5. Correlation Between HER3 mRNA Expression and CDH1 Expression**

- A positive correlation was observed between HER3 mRNA and protein levels in the TMA and COLO data sets (Figure 3).
- There was an overall correlation between EdgeSeq HER3 mRNA data and IHC for HER3 protein (Figure 6).

**Figure 6. Analysis of HER3 Expression in BBSA Subsets**

- **Table 2. HER3 mRNA Expression Patterns Among Cancer Types in the TMA, TCGA, and COLO Data Sets**

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>HER3 mRNA Expression Patterns</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMA HER3 mRNA</td>
<td>Higher scores for genes regulating the cell cycle in cancer tissues than in normal tissues</td>
</tr>
<tr>
<td>TCGA HER2+ TNBC_BL1</td>
<td>Higher scores for genes regulating the cell cycle in cancer tissues than in normal tissues</td>
</tr>
<tr>
<td>COLO HER2+ TNBC_BL2</td>
<td>Higher scores for genes regulating the cell cycle in cancer tissues than in normal tissues</td>
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</table>

- **Figure 7. Correlation Between HER3 and CDH1 mRNA Expression Levels**

- In some cancer types from the TMA data set, almost no HER3 protein expression was detected, despite the presence of unlimited HER3 mRNA expression.

- This pattern was not observed in the COLO data set, suggesting that the lack of protein expression is independent of mRNA expression.