Establishment of a Novel Target ADC Portfolio Derived from Predictive Discovery

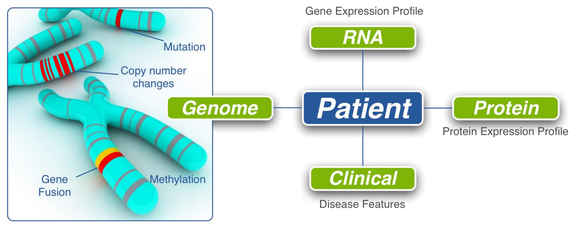
Kyle Hansen, Gady Cojocaru*, Andrew Pow, Andrew Drake, Liat Dassa*, Itay Spector*, Mark White, and Mary Haak-Frendscho
Compugen USA, Inc, South San Francisco, CA, USA and Compugen Ltd*, Tel Aviv, IS

Abstract

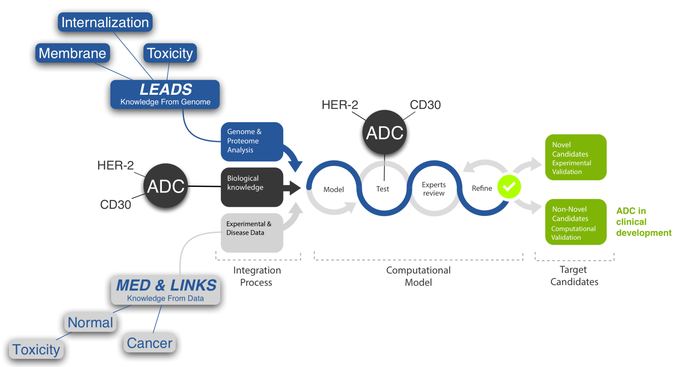
Targeted treatment of solid or liquid tumors with antibody drug conjugates (ADCs) has been shown to lead to significant clinical benefit. However, there is a pronounced need for additional ADC targets for this compelling drug modality. To that end, Compugen has applied its broadly applicable Predictive Discovery infrastructure to identify novel ADC target candidates.

Using our unique discovery platform, we have computationally identified five novel ADC targets with first-in-class therapeutic potential. The query criteria included differential tumor expression, greater than 10% prevalence in tumors with an unmet medical need, membrane localization, and predicted target protein internalization capabilities. Here we will describe an ADC program with potential utility in multiple tumor types. In tumor microarray IHC studies, the target protein shows differential tumor membrane staining with restricted expression in normal tissues. ADC constructs comprised of a target specific monoclonal antibody linked to an auristatin payload possess sub-nanomolar IC_{50} killing when tested in ovarian, stomach and liver tumor cell lines endogenously expressing the target. Xenograft studies are in progress to test in vivo efficacy of ADCs for this program.

Compugen's Discovery Process



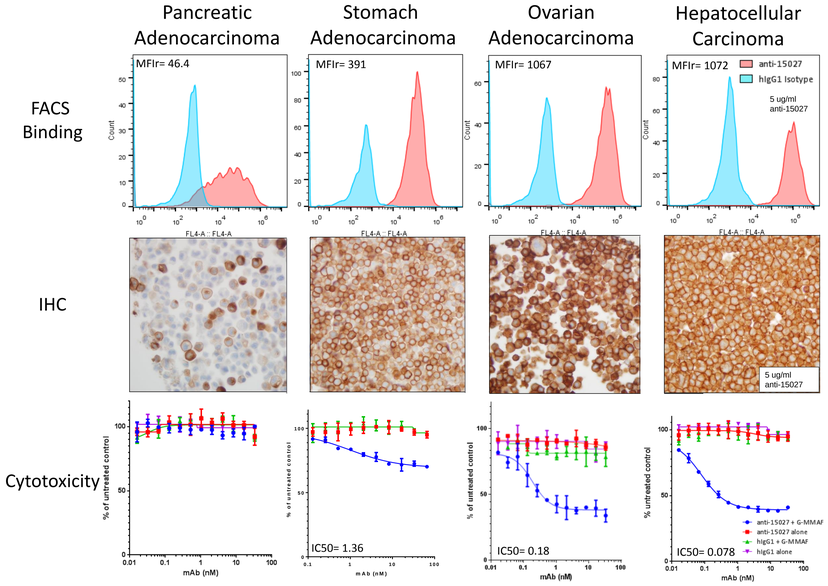
Dataset	Source	Data Type	Tissues
GTEx	Normal	NGS	~ 30 tissue types
TCGA & Others	Cancer	NGS	~ 30 tumor types
CCLE & Others	Cell lines	NGS	< 1000 cell lines
Proprietary MED Platform	Various	Microarray	< 100,000 samples



Five Novel ADC Targets

Program	Target Information	Stage
CGEN-15027	• Type I membrane protein • Differential mRNA expression profile • Overexpressed in multiple cancers	Initiating lead selection activities including in vivo studies; IC50 ≤1nM on multiple cancers
Program B	• Type II membrane protein • Exquisite differential mRNA expression profile • Literature reports disease association	Antibody discovery in progress
Program C	• Type I membrane protein • Potential developmental gene product • Expressed in solid and hematological cancers	Target validation in progress
Program D	• Multiple membrane spanning protein with large extracellular domain • Strong literature support for disease association	Target validation in progress
Program E	• Type I membrane protein • Reasonable differential mRNA expression profile • Present on 7% of cancers	Ongoing computational analysis

CGEN-15027 ADC

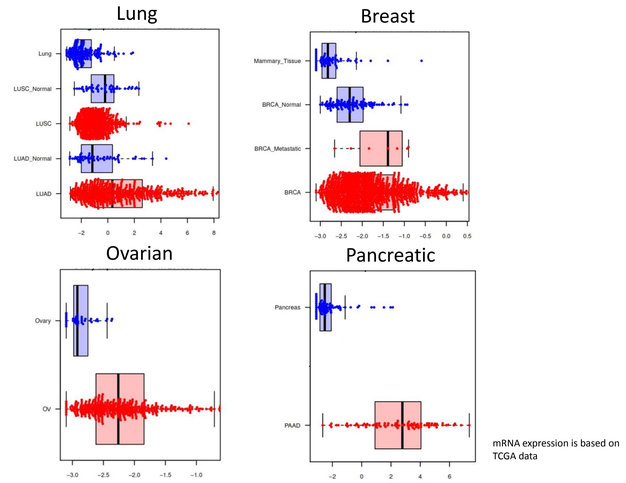


Results shown are from "Piggyback" cytotoxicity assays using protein G coupled to MMAF as a secondary.

Cancer Cell Line Type	CGEN-15027 Transcript (RNAseq)	Copy Number	Cytotoxic Activity (IC50, nM)
Hepatocellular Carcinoma	128.51	381,929	0.12
Hepatocellular Carcinoma	74.37	465,242	0.078
Ovarian Adenocarcinoma	32.02	403,466	0.18
Stomach Adenocarcinoma	21.06	126,035	1.36
Pancreatic Adenocarcinoma	25.72	20,767	N/A

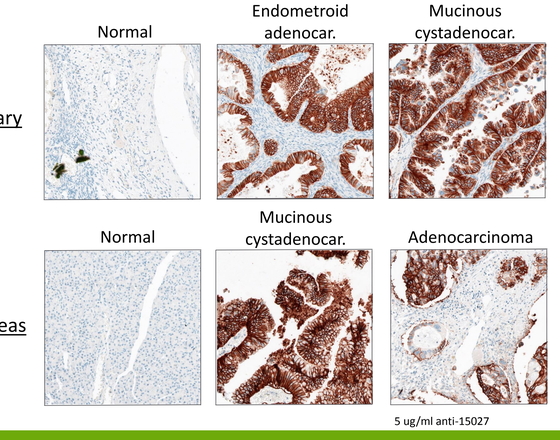
CGEN-15027 Expression

CGEN 15027 mRNA Expression in Multiple Cancers



mRNA expression is based on TCGA data

CGEN 15027 Protein Expression in Multiple Cancers



Summary

- Five novel ADC targets discovered computationally
  - Known ADC targets "discovered" in query, validating approach
  - Differential tumor expression suitable for ADCs
  - Predicted target internalization
  - Present on multiple tumor types
- CGEN-15027 demonstrates sub-nanomolar IC50s in multiple tumor cell lines
  - In vivo xenograft studies initiated
- Additional four novel programs in various stages of drug discovery and target validation