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COMPUTATIONAL DISCOVERY AND EXPERIMENTAL VALIDATION OF CGEN-15032 AS A NOVEL TARGET FOR CANCER IMMUNOTHERAPY

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INTRODUCTION

GENE STRUCTURE HOMOLOGY HIGHLIGHTS CGEN-15032 AS A NOVEL IMMUNE CHECKPOINT

Antibody blockade of CTLA4 and PD-1 immune checkpoints emerged as an effective treatment modality for cancer. However, most patients do not achieve sustained benefit, suggesting a need for targeting of additional immune checkpoints. Towards prediction of novel immune checkpoints, we developed a set of computational tools including gene structure alignment for the identification of functional homologs for B7/CD28 genes in the absence of sequence similarity. This discovery platform has been tested and validated extensively and has demonstrated its validity by identifying novel immune checkpoints such as TIGIT and PVRIG, which are currently in preclinical development by Compugen. This predictive platform was employed to identify an additional immuno-modulatory target, designated CGEN-15032.

CGEN-15032 IS EXPRESSED IN THE TUMOR MICRO-ENVIRONMENT AND INHIBITS T CELL ACTIVATION

CGEN-15032 is expressed on cancer cells and on the myeloid component of immune infiltrate within the tumor microenvironment. Several human and mouse in vitro experimental systems have demonstrated an immune-modulatory effect for CGEN-15032. Ectopically expressed CGEN-15032 dampened anti-melanoma activity of tumor-infiltrating lymphocytes, derived from melanoma patients. In line with the effect observed in human system, over expression of murine CGEN-15032 in artificial antigen-presenting cells resulted in reduced activity of TCR-transgenic DO11.10 T cells. These functional data, in conjunction with the expression of 15032 on myeloid and tumor cells, suggest that 15032 is a ligand and part of a novel pathway that inhibits T cell function.

CGEN-15032 GENE KO RESULTS IN DELAYED TUMOR GROWTH IN VIVO

To study the immuno-modulatory function of CGEN-15032 and its role in anti-cancer immunity, we generated CGEN-15032 knock-out (KO) mice. MC38 tumors grew slower in CGEN-15032 KO relative to wild-type mice (in average 47%, $p<0.01$). Furthermore, a combinatorial treatment of CGEN-15032 deficient mice with anti-PDL1 antibody resulted in tumor growth inhibition compared with anti-PDL1 treated wild-type mice (in average 40%, $p<0.05$).
Taken together, these data provide experimental validation of our computational discovery approach and highlight CGEN-15032 as an attractive target for cancer immunotherapy.

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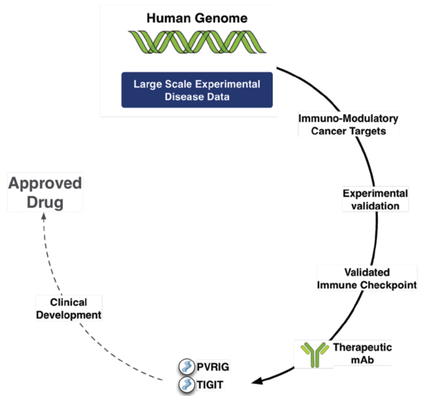
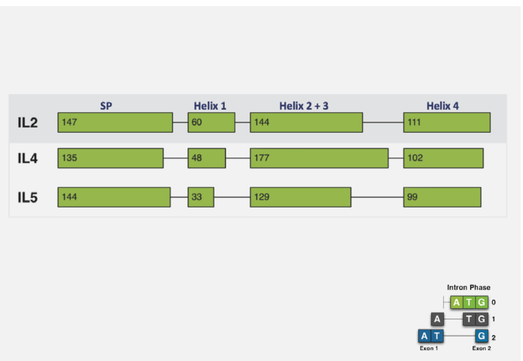


DISCOVERY OF NOVEL IMMUNE CHECK-POINTS

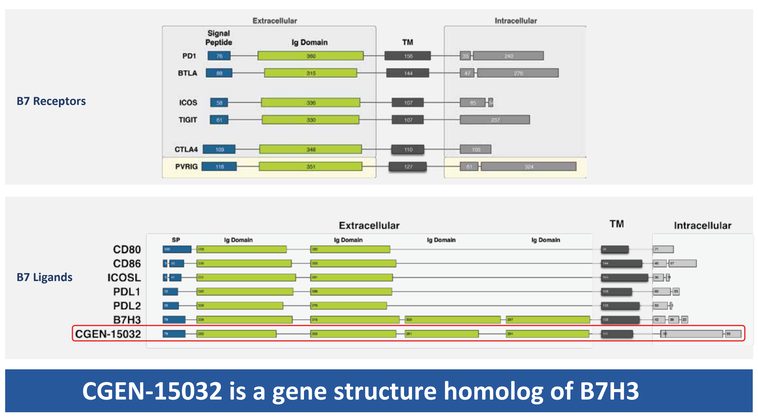
For Some Immune Genes, Gene Structure is More Conserved Than Sequence.

IL2 and PD1 have no sequence homologs

Both share gene structure homology with functionally related genes



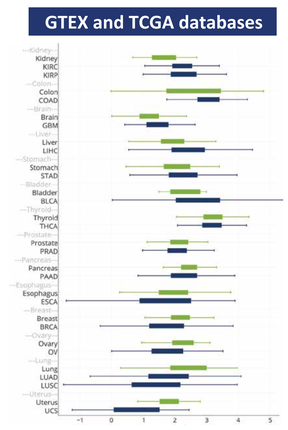
15032 WAS DISCOVERED BY GENE STRUCTURE HOMOLOGY



CGEN-15032 is a gene structure homolog of B7H3

CGEN-15032 RNA IS EXPRESSED SIMILARLY ACROSS HUMAN NORMAL AND CANCER TISSUES

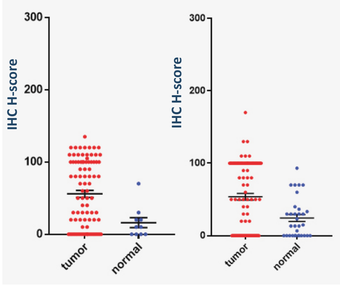
- Expressed in many tumor types and normal tissues
- No substantial normal vs. cancer differential expression at RNA level
- Expressed on epithelial and endothelial cells as well as immune-cell sub-sets
- Epithelial expression is similar to B7H3 and CEACAM1



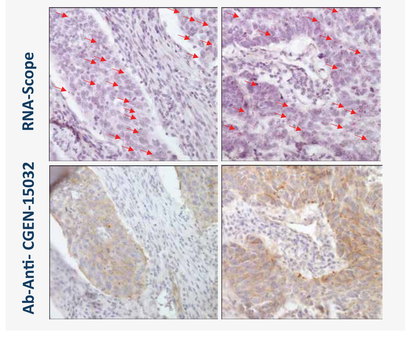
CGEN-15032 EXPRESSION AT PROTEIN LEVEL IS HIGHER IN NSCLC RELATIVE TO NORMAL LUNG TISSUES

Study 1
110 cancer
10 normal

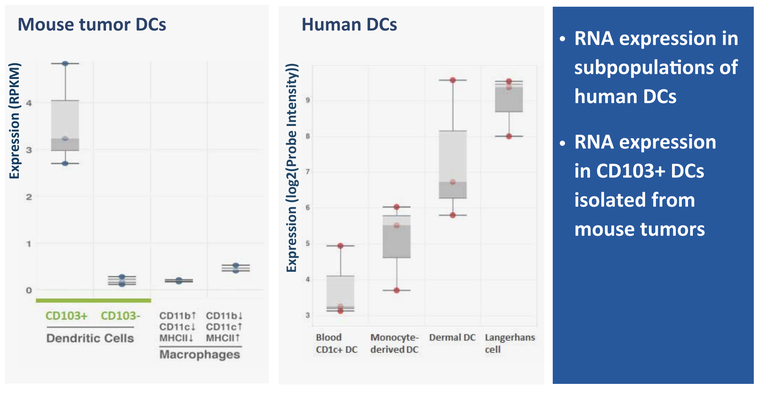
Study 2
111 cancer
32 normal



Serial sections of NSCLC tissue stained with CGEN-15032 RNAscope probe and CGEN-15032 Ab

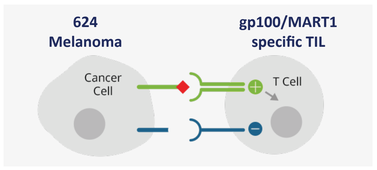


EXPRESSION OF CGEN-15032 IN HUMAN AND MOUSE DENDRITIC CELLS (DCs)

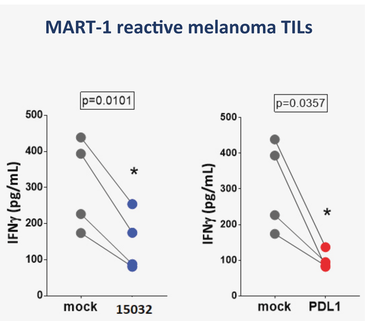


- **RNA expression in subpopulations of human DCs**
- **RNA expression in CD103+ DCs isolated from mouse tumors**

CGEN-15032 INHIBITS TUMOR INFILTRATING LYMPHOCYTE (TIL) ACTIVITY SIMILAR TO PDL1



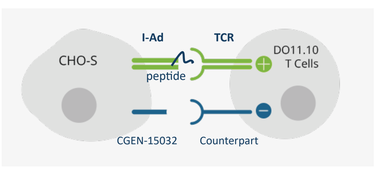
MART-1 reactive melanoma TILs

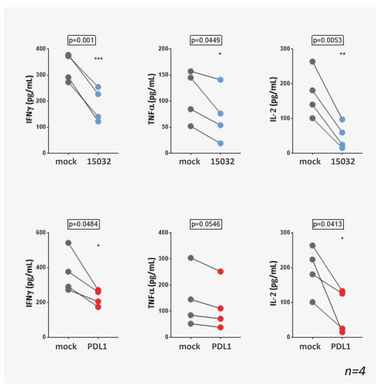


CGEN-15032 over expression on melanoma cells dampens Ag-specific activation of TILs

- Similar effects observed in 3 additional TILs
- Similar effects observed with additional read-outs (TNFα, IL2, proliferation and activation markers)

CGEN-15032 INHIBITS Ag-SPECIFIC ACTIVATION OF MURINE CD4 T CELL

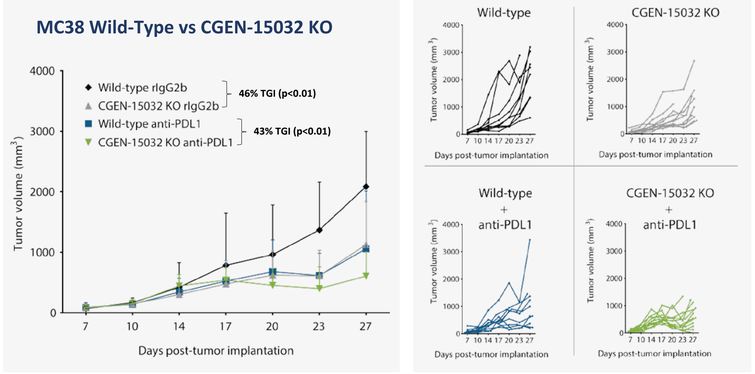




CGEN-15032 over expression on CHO-S-IAd cells dampens CD4+ DO11 T cell function

- Similar effects observed with additional read-outs (TNFa and IL2)

DELAYED MC38 TUMOR GROWTH IN CGEN-15032 KO MICE



Ganguly and Pardoll, Johns Hopkins University

SUMMARY

- CGEN-15032 is a novel target identified by the immune checkpoint functional homology computational platform
- Expression analysis reveals broad expression on epithelial and endothelial cells as well as specific sub-sets of dendritic cells
- In vitro checkpoint activity demonstrated in human and mouse experimental systems
- In vivo tumor growth inhibition demonstrated with CGEN-15032 KO mice, both alone and in combination with anti-PDL1 treatment
- Human and mouse surrogate antibodies being generated