

# Functional characterization of CDX-1140, a novel CD40 antibody agonist for cancer immunotherapy

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## Introduction

CD40 represents a unique target for immunotherapy due to its powerful effect on multiple relevant cell types:

- CD40 activation on DCs promotes their conversion to APCs that are efficient for stimulation of T cell responses
- CD40 activation on macrophages promotes their ability to mediate effector function such as phagocytosis
- CD40 activation on B cells promotes proliferation and antigen presentation
- CD40 activation on malignant B cells leads to tumor growth inhibition and rejection in xenograft models

Functional aspects of CD40 agonist antibodies will substantially influence its activity profile:

- Block/not block natural ligand (CD40L) interaction
- Promote/lack Fc receptor interaction
- Require/not require FcR binding for agonistic function
- Potency of agonistic activity

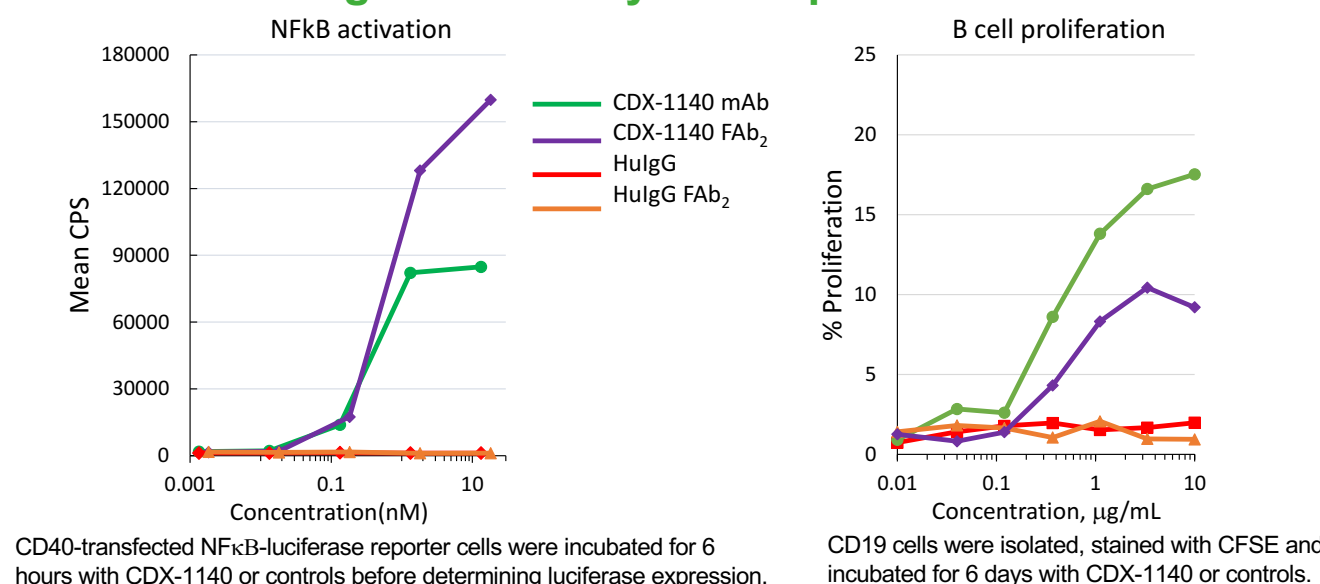
CDX-1140 represents a novel CD40 agonist antibody with unique properties. Comparisons are presented with CP-870,893 also known as clone 21.4.1 (US patent 8388971)

## Making and Characterization of CDX-1140

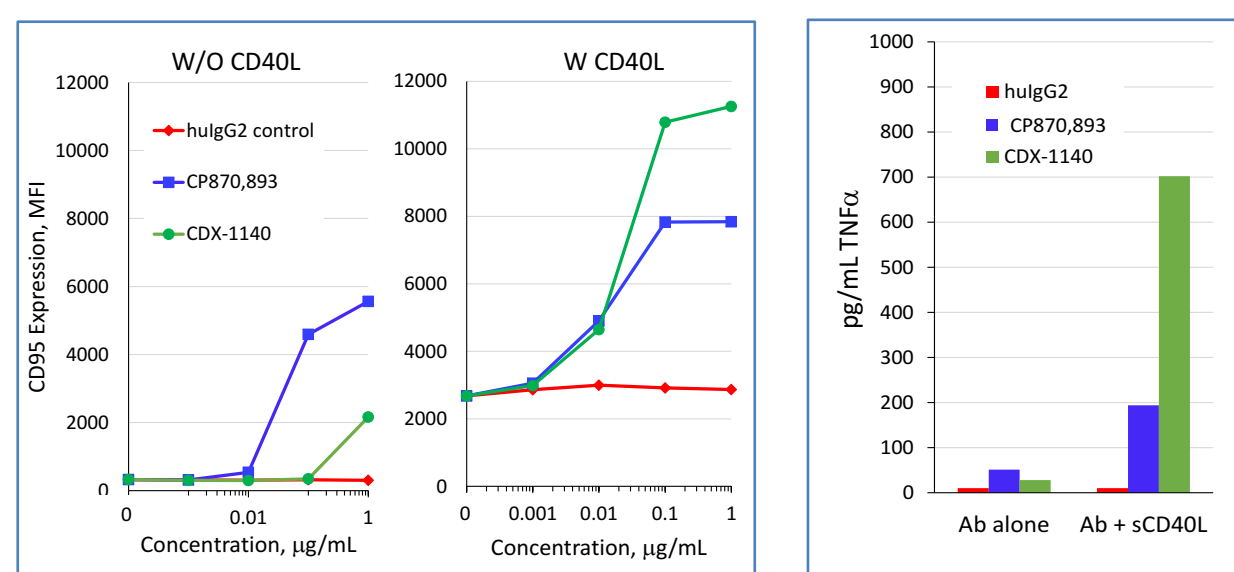
Anti-CD40 monoclonal antibodies (mAbs) were generated by immunization of human Ig transgenic mice (H2L2 strain of Harbour® transgenic mice) with recombinant and cell surface expressed human CD40. Hybridomas were selected using a reporter cell assay engineered to express CD40 and NFκB-responsive luciferase. The variable regions of lead antibodies were cloned in human IgG1 or IgG2 constant domains and expressed in CHO cells. From this panel, CDX-1140, a human IgG2 antibody, was selected for further development.

## CDX-1140: Agonist Activity

### Agonist activity is independent of Fc

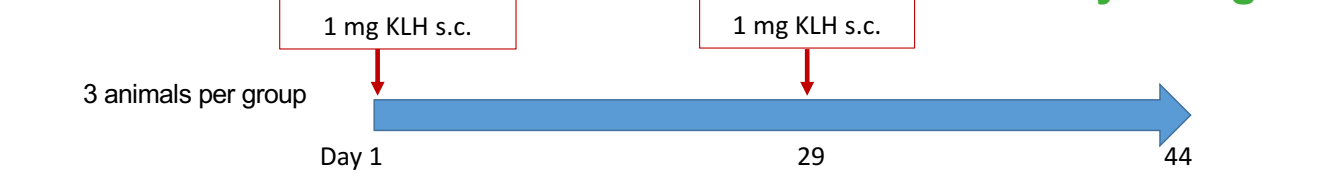


### CD40L enhances CDX-1140 agonist activity

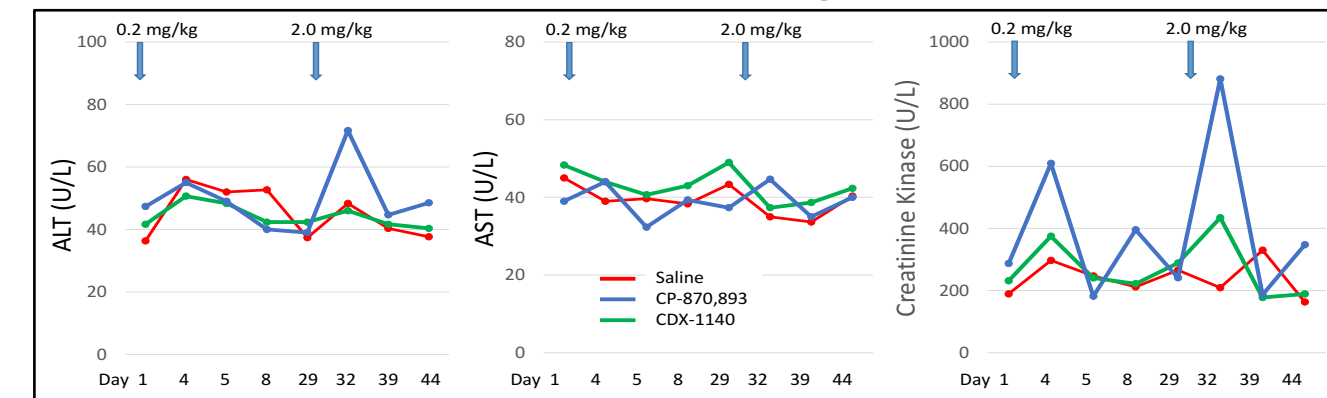


## CDX-1140: Non-human Primate Pilot Study

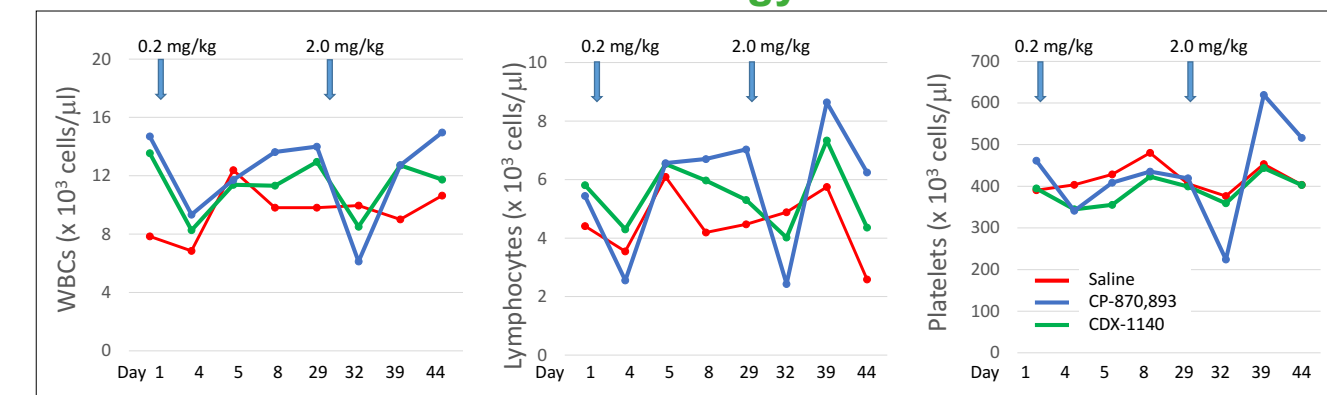
### Study Design



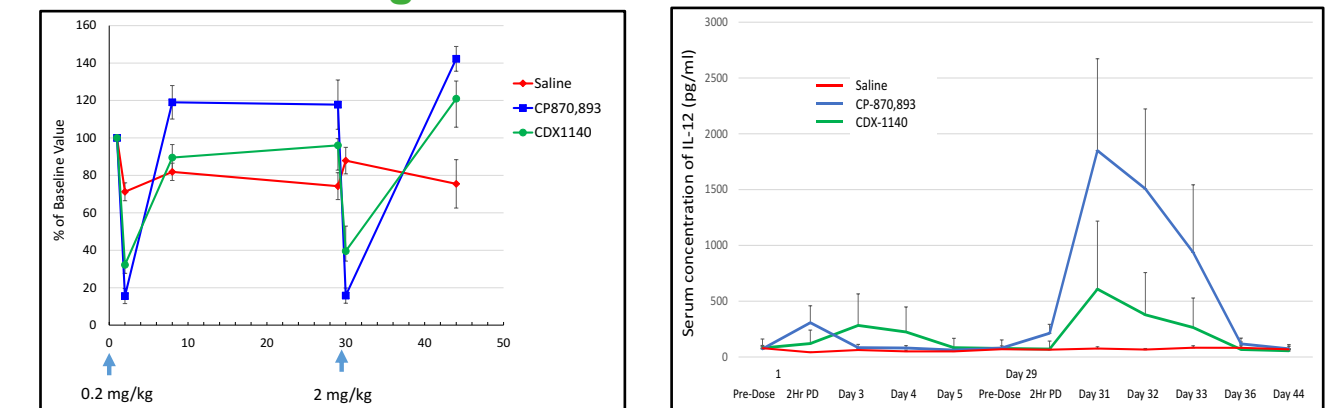
### Clinical chemistry



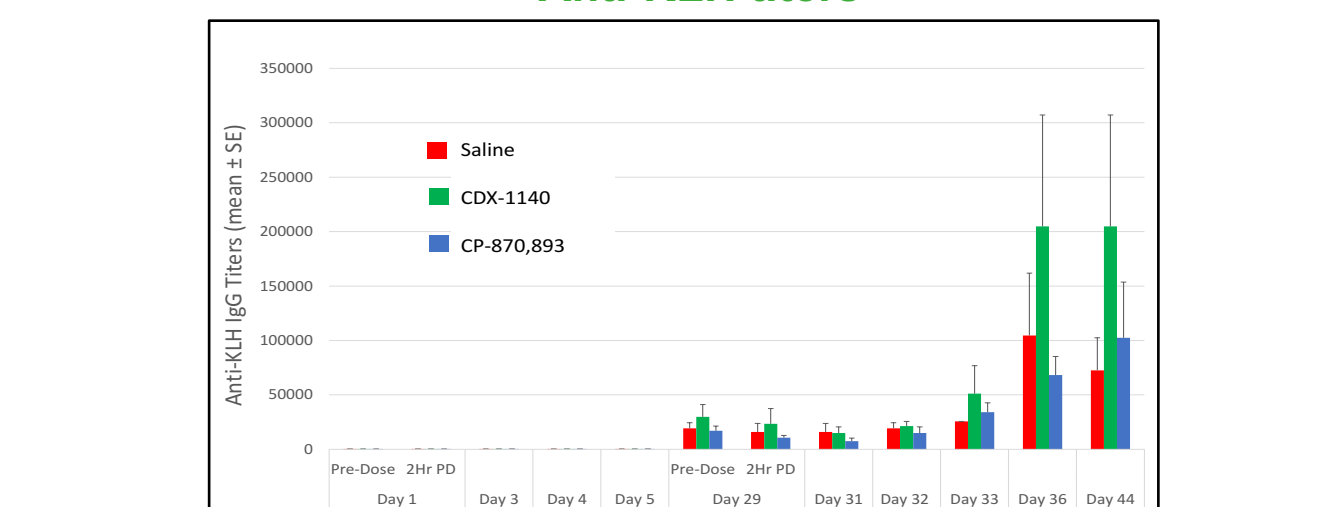
### Hematology



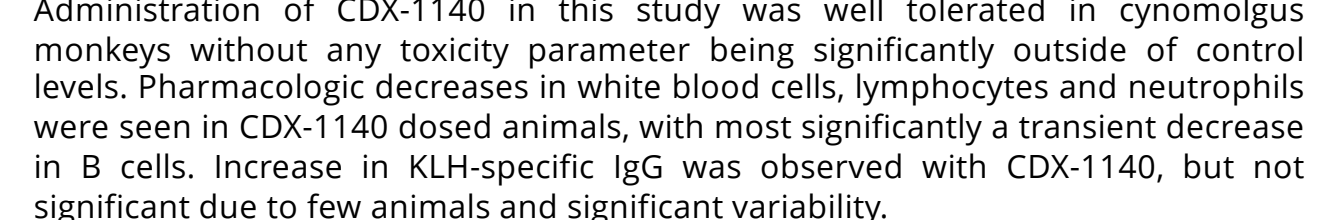
### Circulating B cells



### Serum IL-12



### Anti-KLH titers



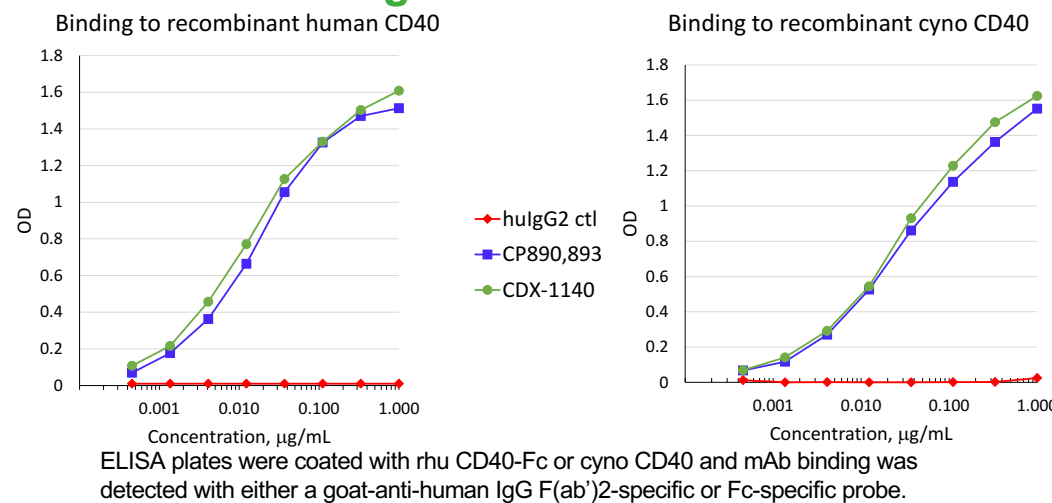
Administration of CDX-1140 in this study was well tolerated in cynomolgus monkeys without any toxicity parameter being significantly outside of control levels. Pharmacologic decreases in white blood cells, lymphocytes and neutrophils were seen in CDX-1140 dosed animals, with most significantly a transient decrease in B cells. Increase in KLH-specific IgG was observed with CDX-1140, but not significant due to few animals and significant variability.

## Conclusions and Next Steps

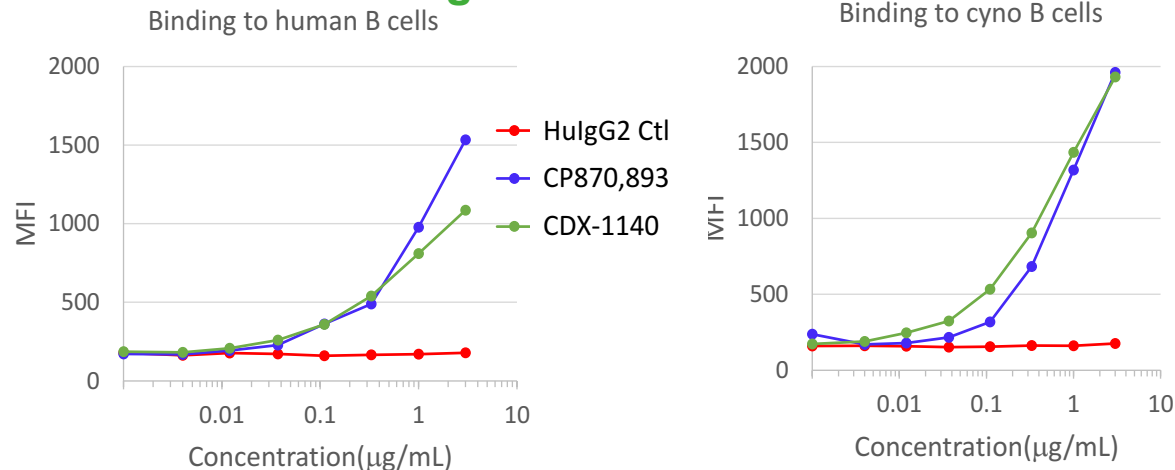
- CDX-1140 represents a novel CD40 agonist antibody with a unique profile:
  - Potent agonist that functions independent of FcR interactions
  - Strong cooperation with CD40L for enhanced activity
  - Direct anti-lymphoma activity in vivo
  - Pharmacologic activity in monkeys minimal evidence of toxicity
- CDX-1140 manufacturing and IND-enabling studies are on-going
- A Phase 1 Study with CDX-1140 in advanced cancer patients is planned to initiate in 2017
- Following dose escalation of CDX-1140, combinations will be explored with immunotherapy and conventional therapies



### Binding to recombinant CD40

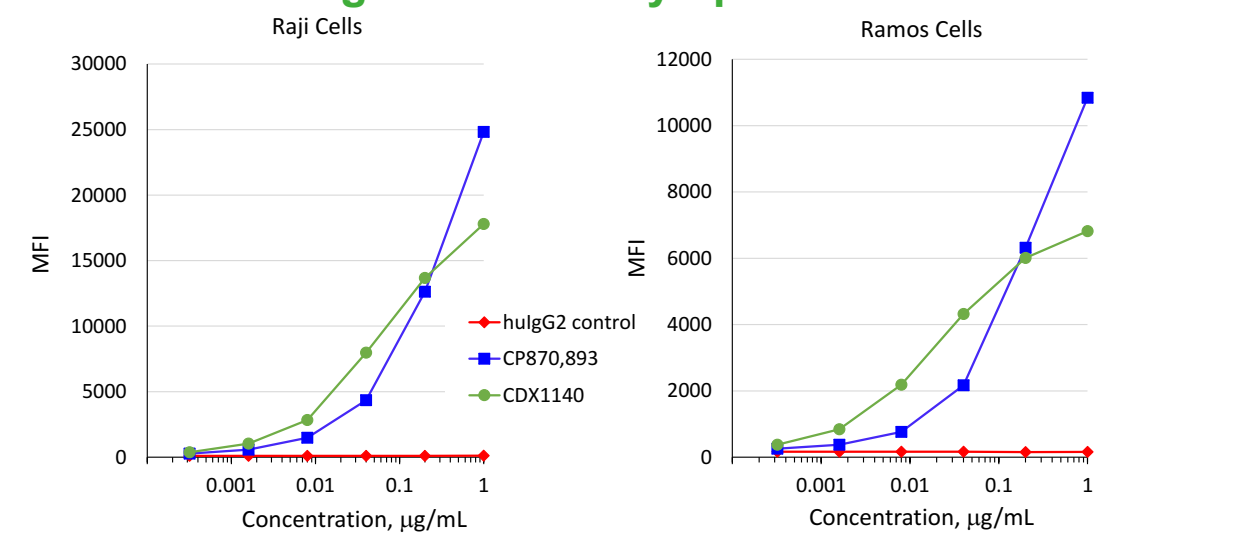


### Binding to CD40 on B cells

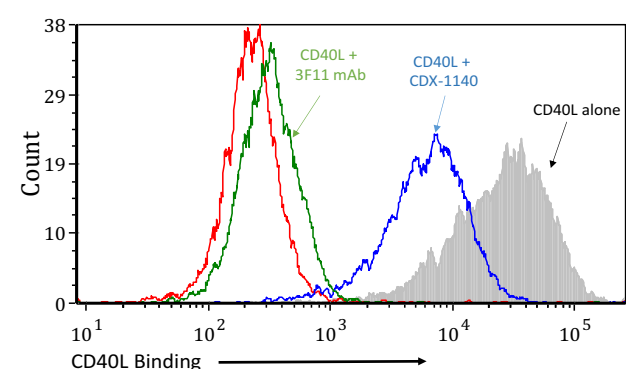


Human or cyno whole blood was incubated with FITC-CDX-1140. B cells were identified by subsequent staining with anti-CD20.

### Binding to CD40 on lymphoma cell lines

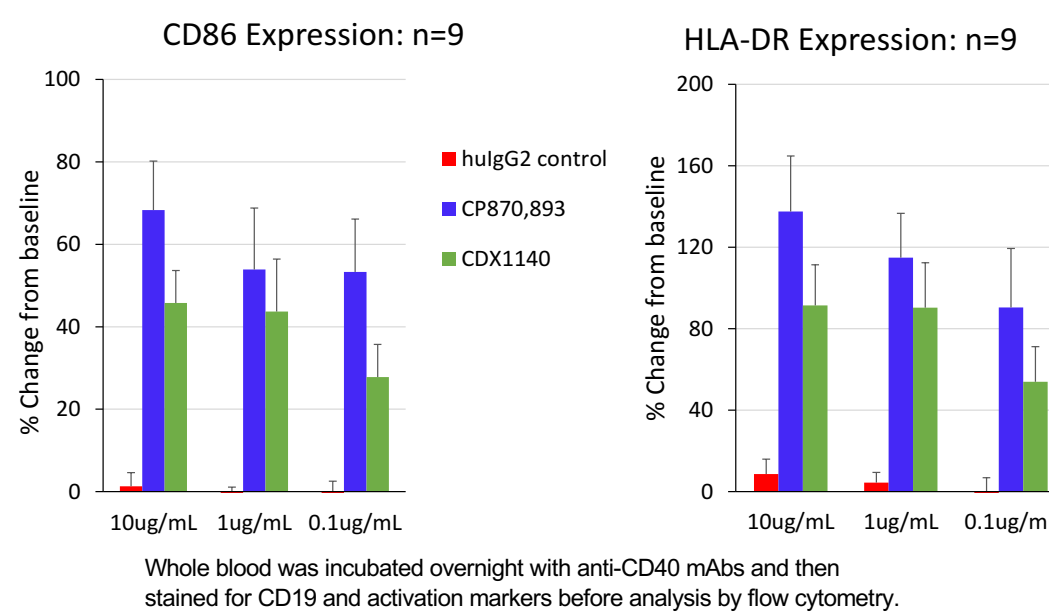


### CDX-1140 does not block CD40L binding

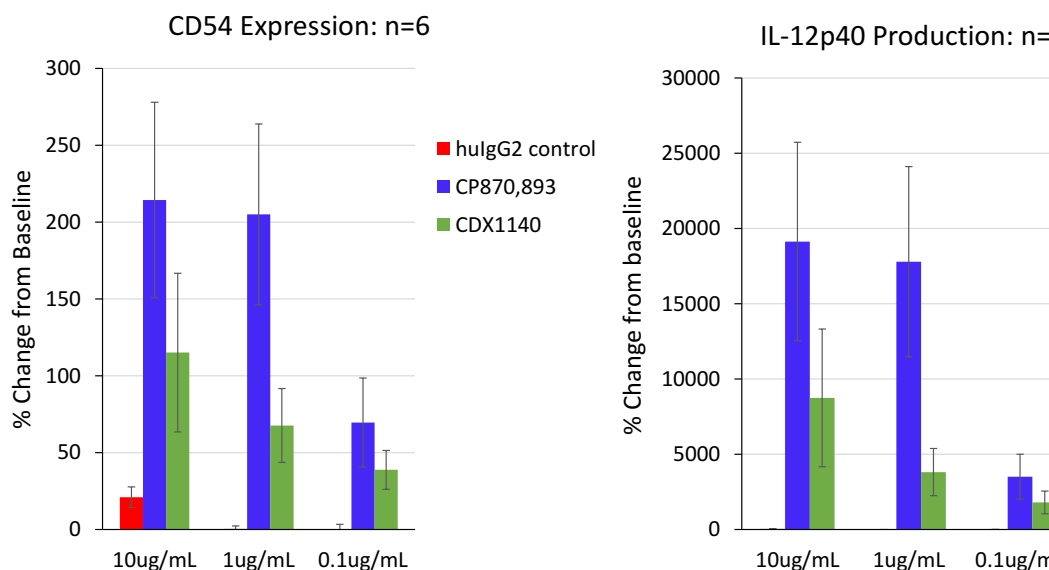


Competition with labeled CD40L for binding to CD40L on the hCD40 transfected 293 cells as measured by flow cytometry. 3F11 is an anti-CD40 mAb that binds the ligand binding domain of CD40.

### Activation of B cells in whole blood



### DC activation



## CDX-1140: Activity in Lymphoma Model

