

FIG. 1: Targeting the latent form of TGFβ1 provides isoform and context specificity

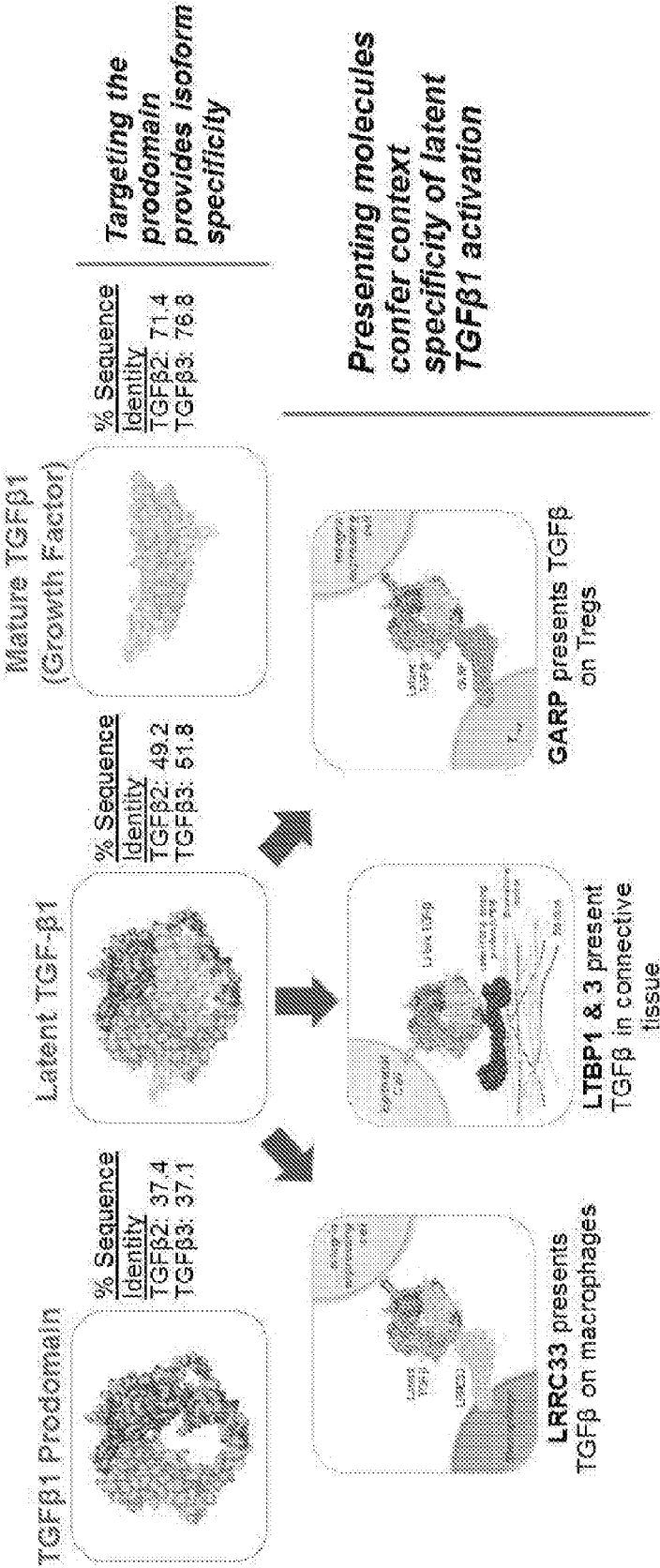


FIG. 2A: In Vitro Binding Profile of a Context-Independent Antibody (SR-AB1) Against proTGFβ1

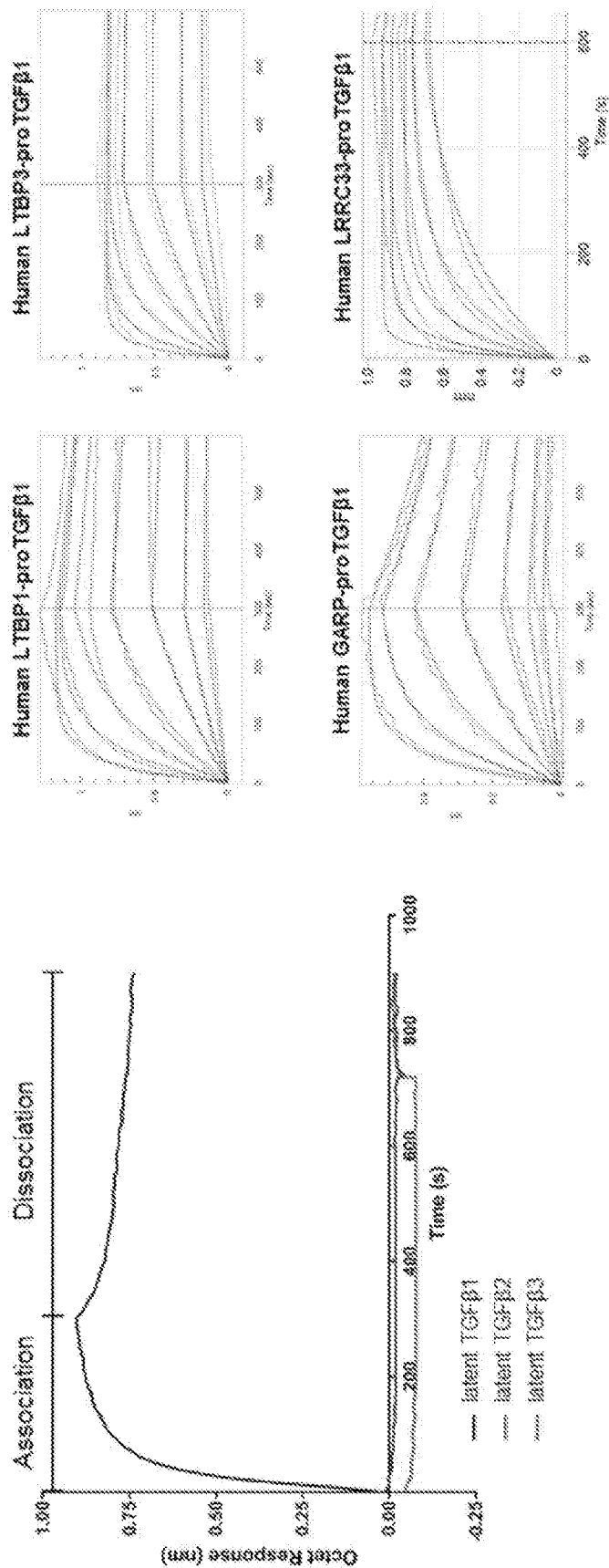


FIG. 2B: In Vitro Binding Profile of a Context-Selective Antibody (SR-AB2) Against LTBP1-proTGFβ1

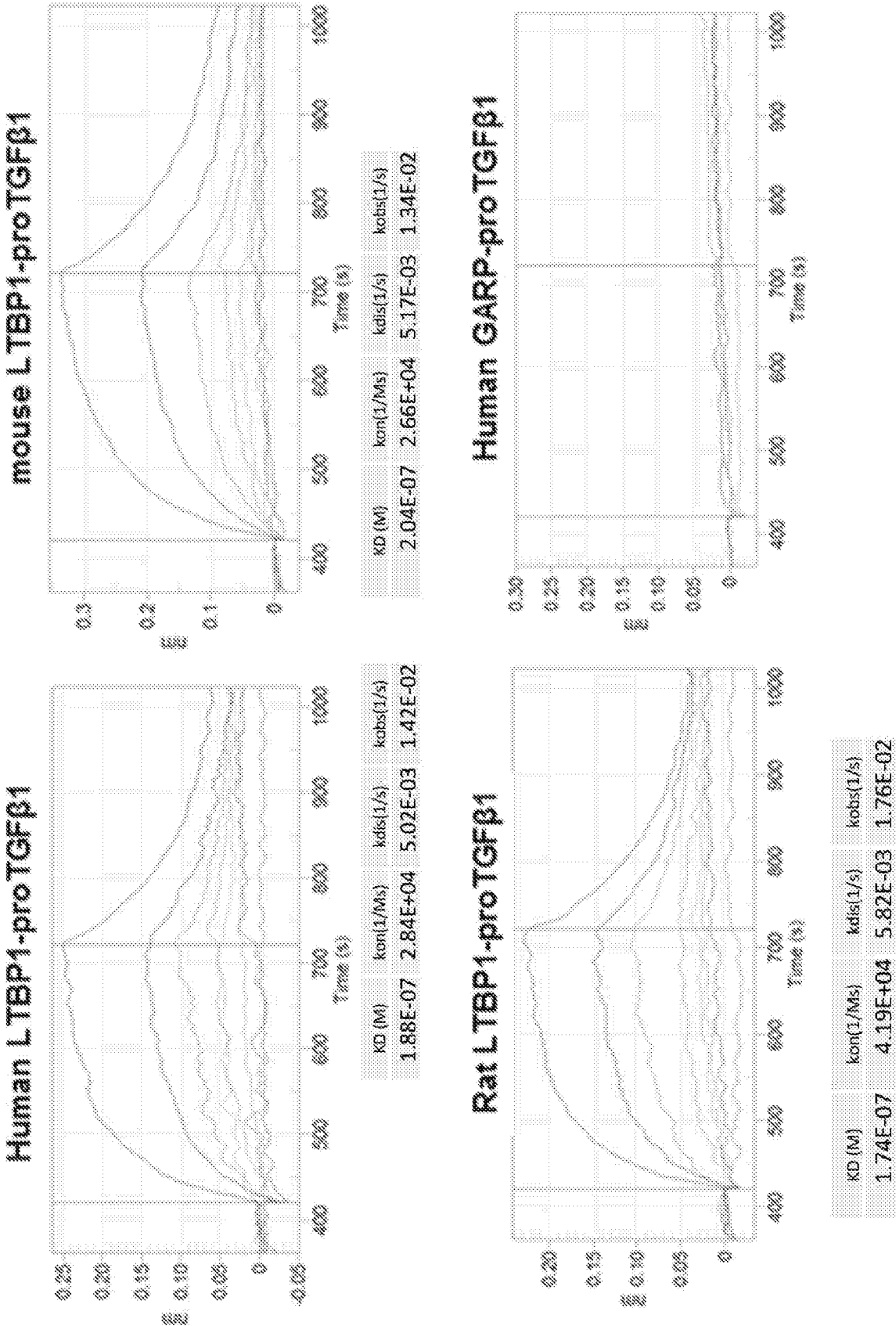


FIG. 3A: Cell-Based Assays for Detecting ECM-associated TGFβ Activation

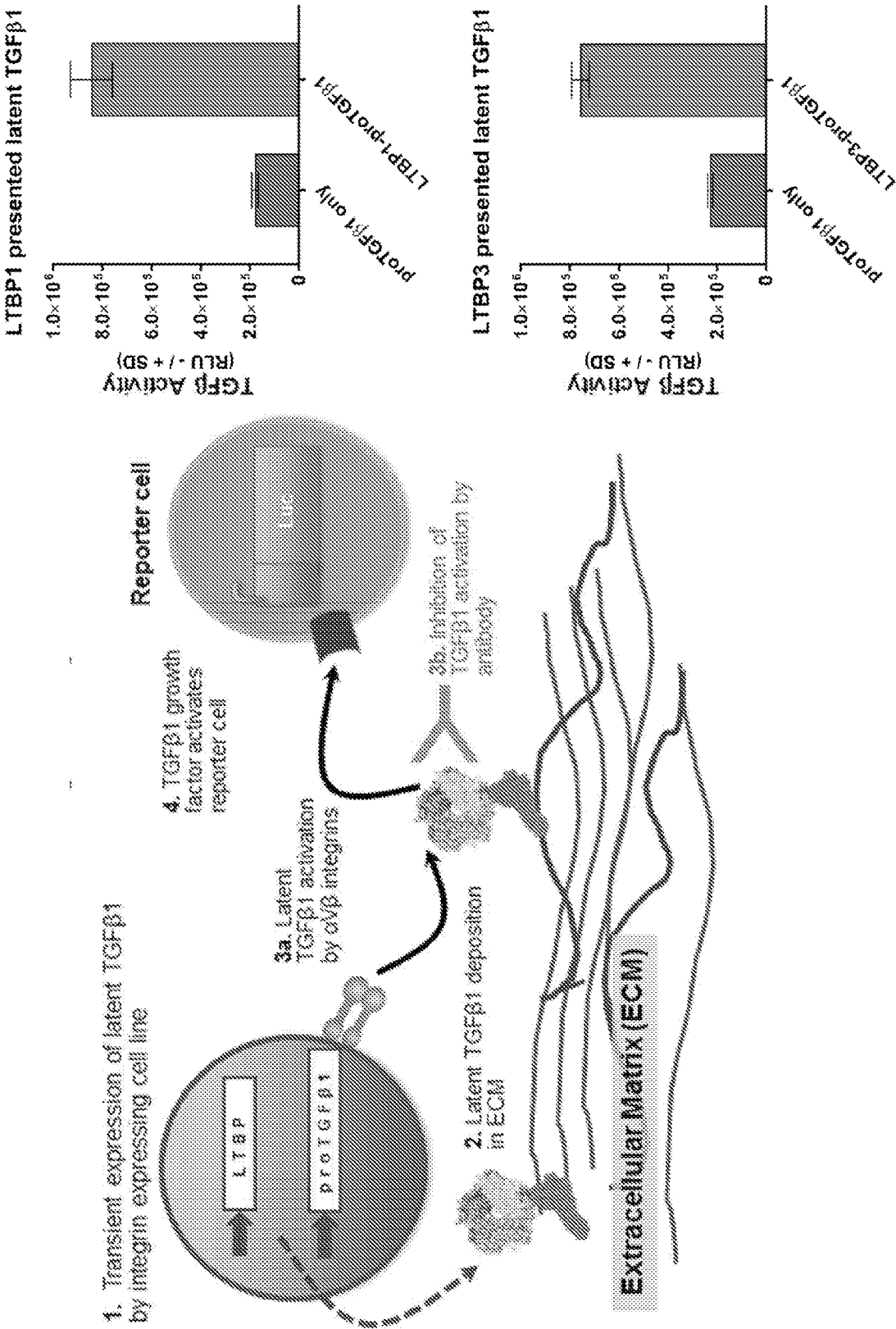
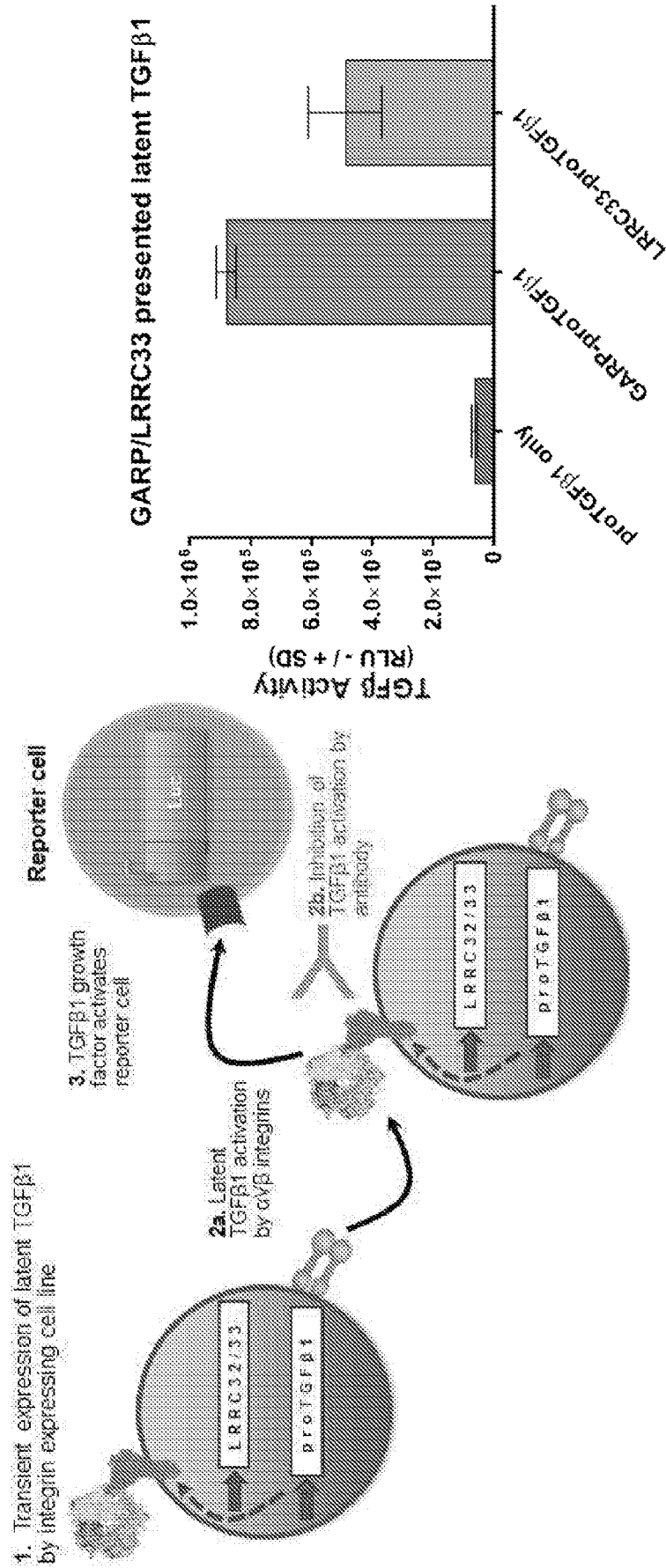


FIG. 3B: Cell-based Assays for Detecting Cell Surface TGFβ Activation



Optimization of Cell-Based Potency Assays

FIG. 4A

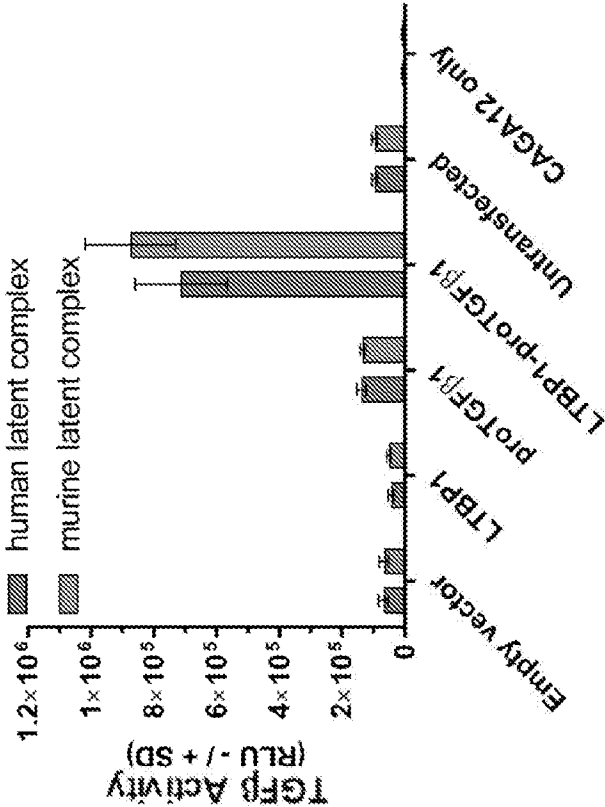


FIG. 4B

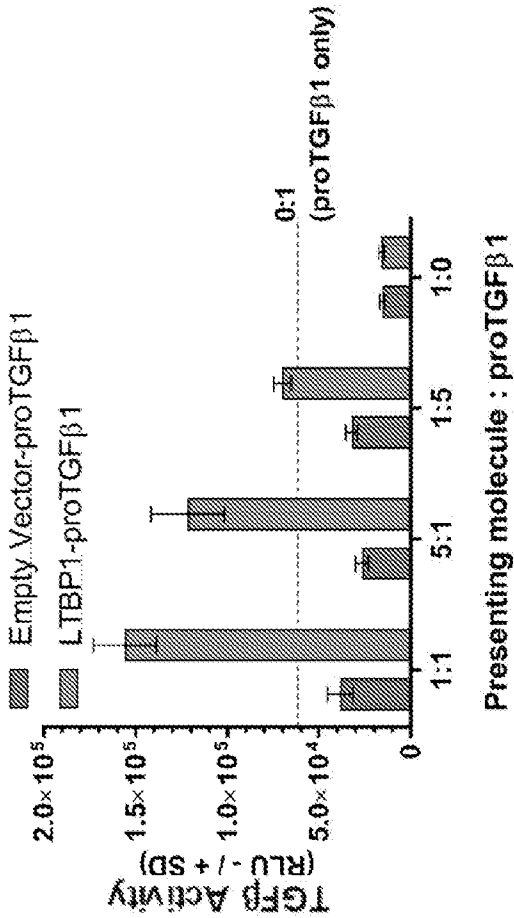


FIG. 5: Fibronectin promotes integrin activation of LTBP-presented latent TGFβ1

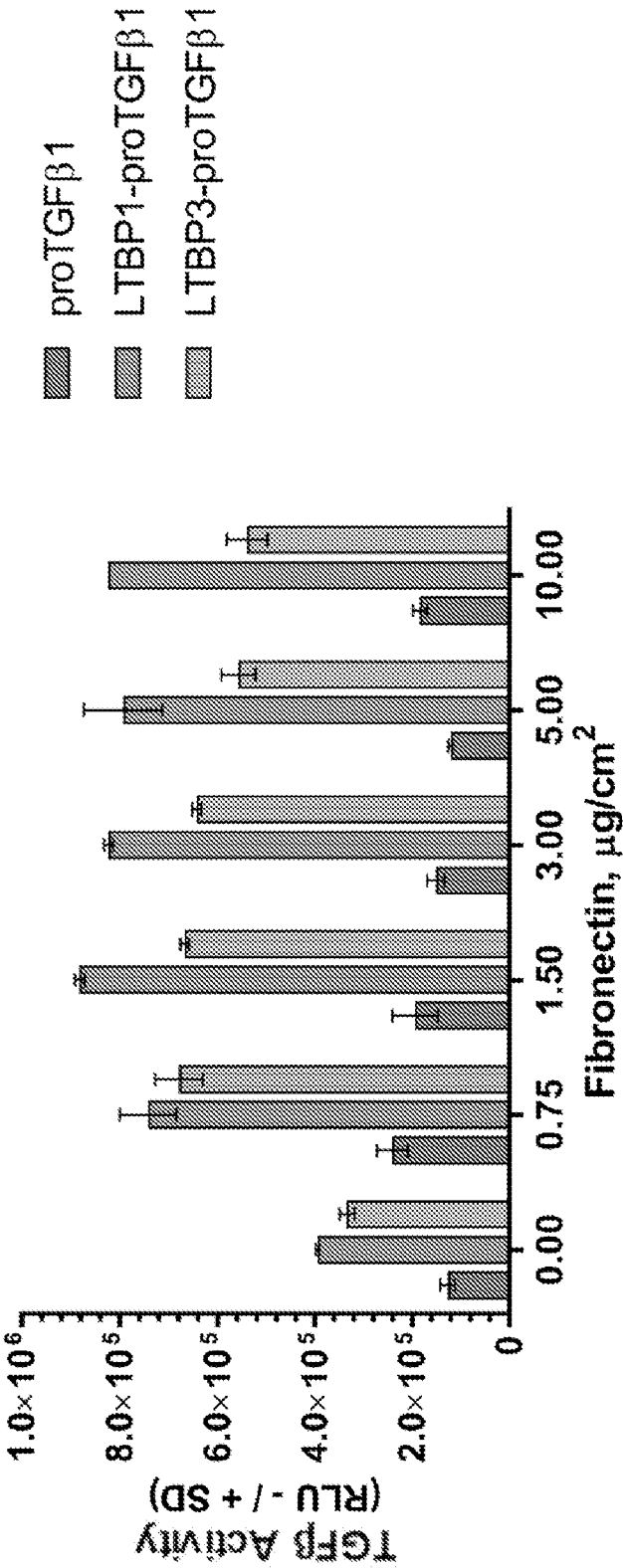
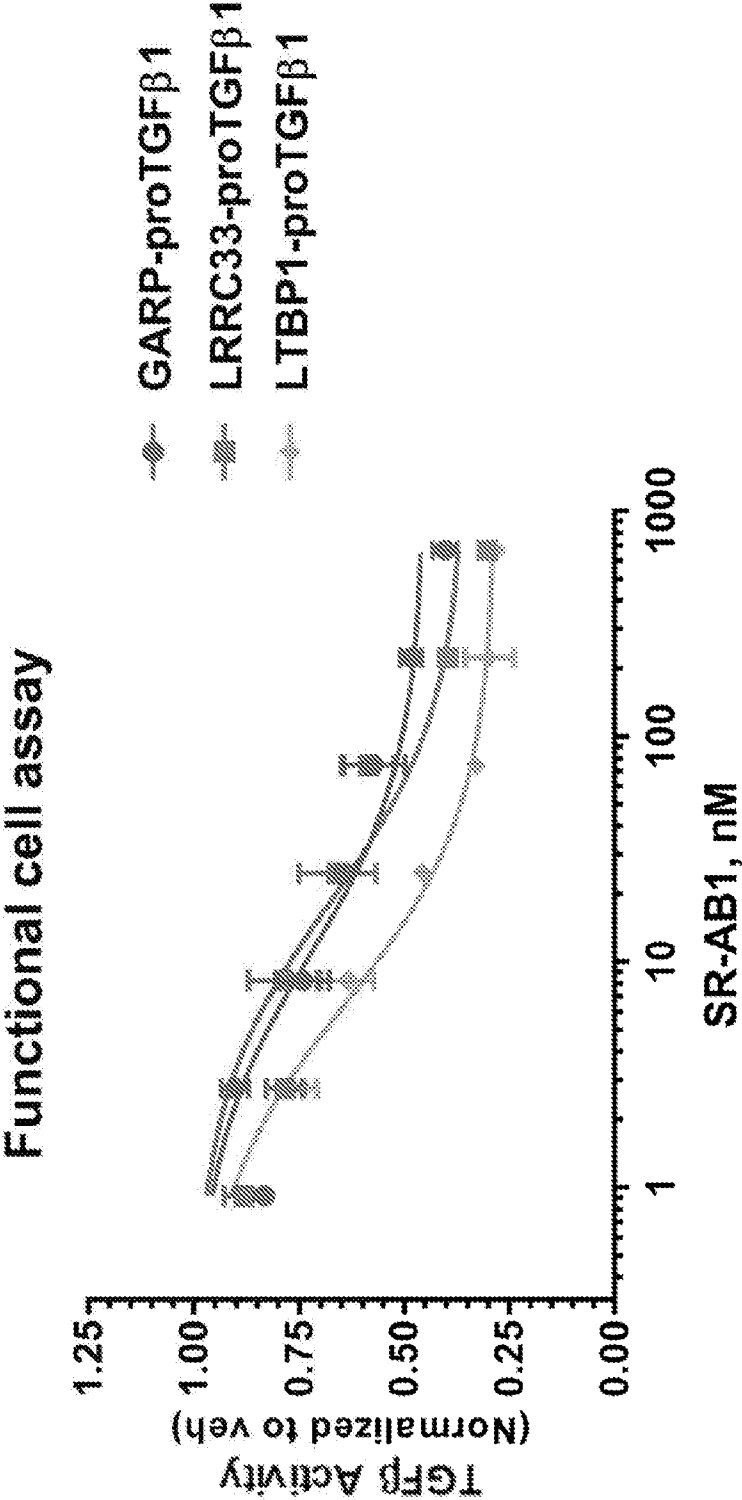


FIG. 6: SR-AB1 Inhibits Integrin-Mediated Activation of Matrix-Associated and Cell-Associated TGFβ1



SR-AB2 selectively binds and inhibits LTBP1/3-Associated proTGFβ1

FIG. 7A Anti-LTBP-proTGFβ1 ELISA

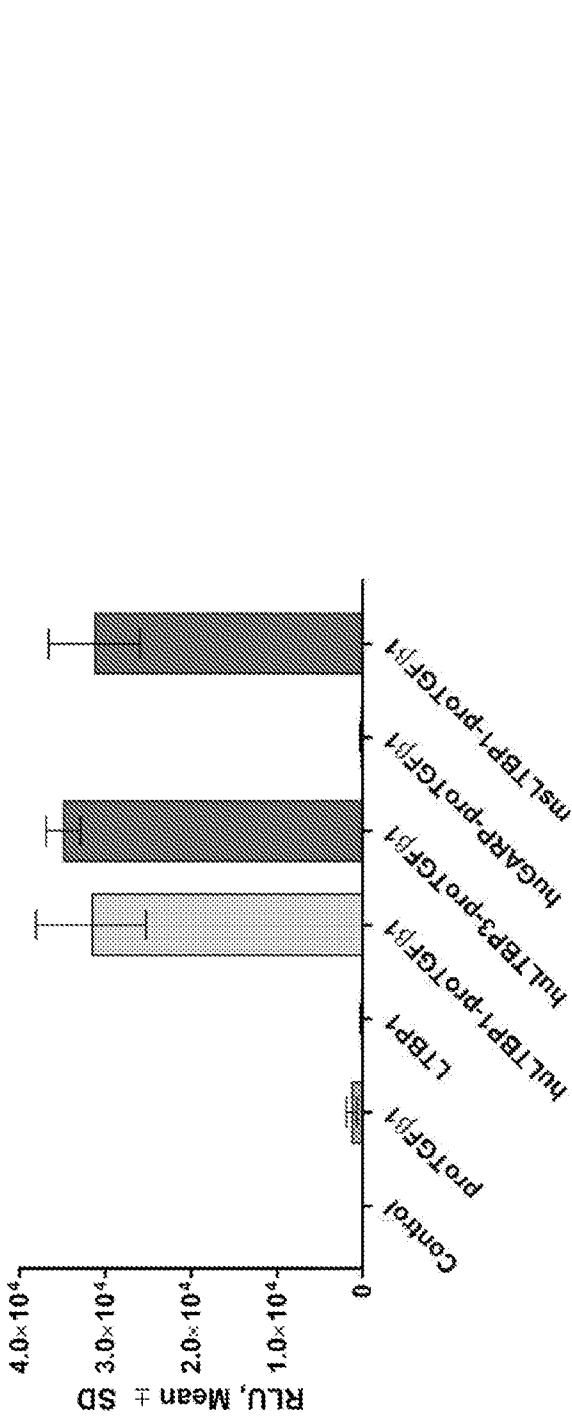


FIG. 7B LTBP1-proTGFβ1 (human/mouse)

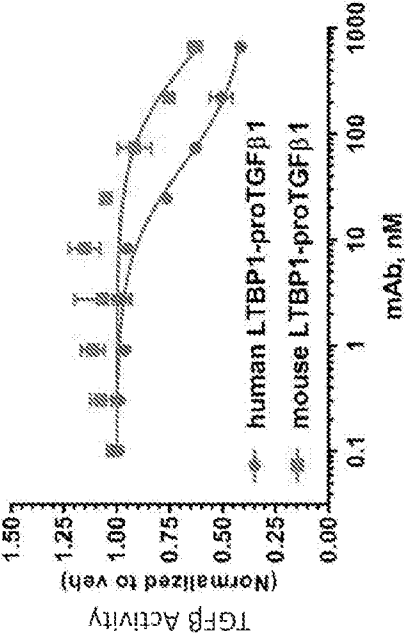


FIG. 7C LTBP3-proTGFβ1

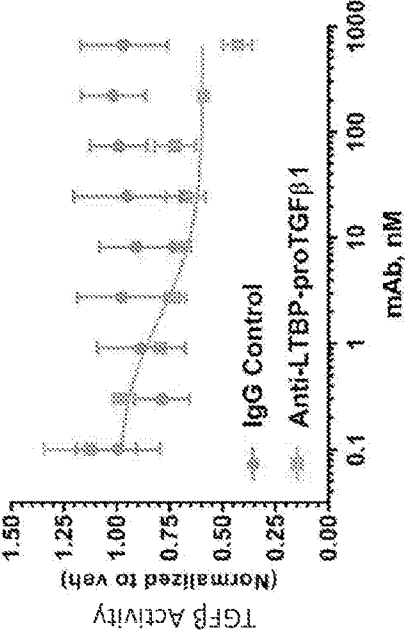


FIG. 8: SR-AB2 Variable Region Sequence

VH:

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWYRQAPGQGLEWMGWISAYNGNTINYAQKLQGRVTMTTDTSTAYMELSLRSDDTAVVYCARAPLGNFDSWGQGTMTVTVSS

CDRH1

CDRH2

CDRH3

VLambda:

NFMLTQPHSVSESPGKTVTISCTRSSGSIASNYYQWYQQRPQSSPTTVIYEDNQRPQSGVDRFSGSIDSSNSASLTISGLKTEDEADYYCQSYDSSNHPVVFGGGTKLTVL

CDRL1

CDRL2

CDRL3

FIG. 9: SR-AB2 Specifically Binds to proTGFβ1:LTBP1 & 3 Complexes

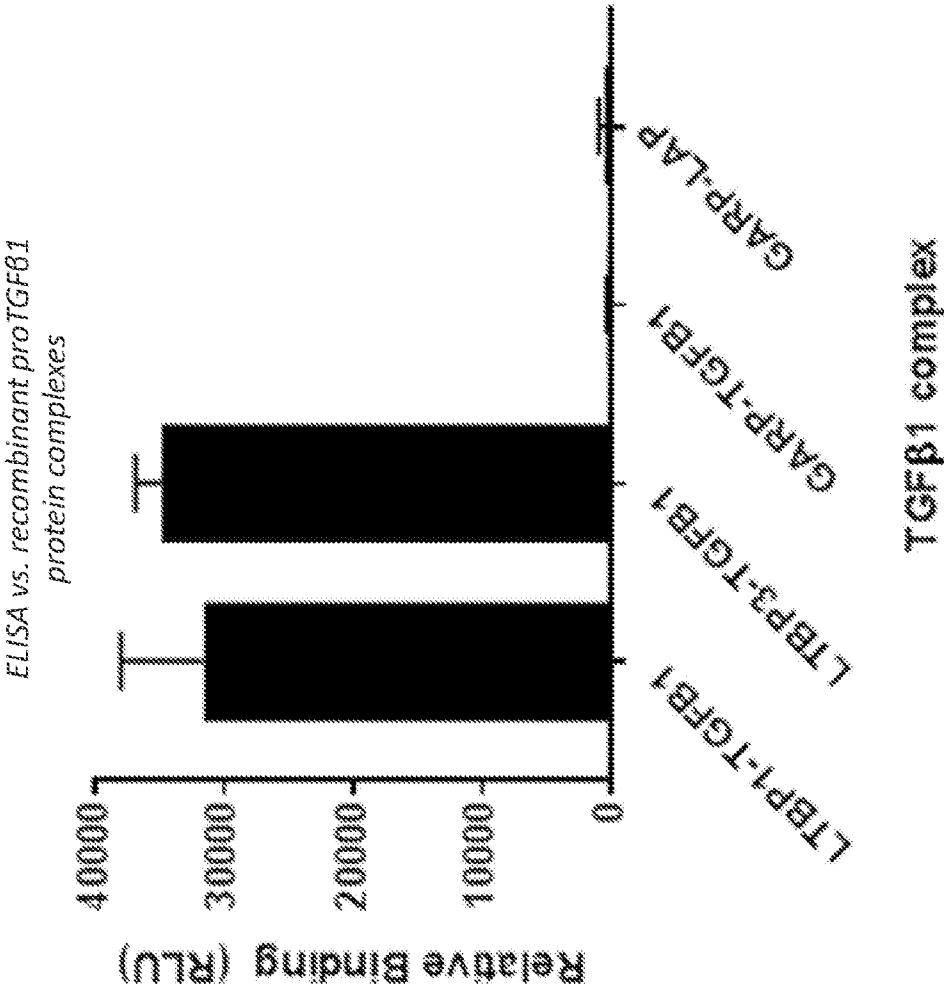


FIG. 10A: SR-AB2 Selectively Inhibits Activation of Matrix-Associated, but not GARP-Associated, proTGFβ1

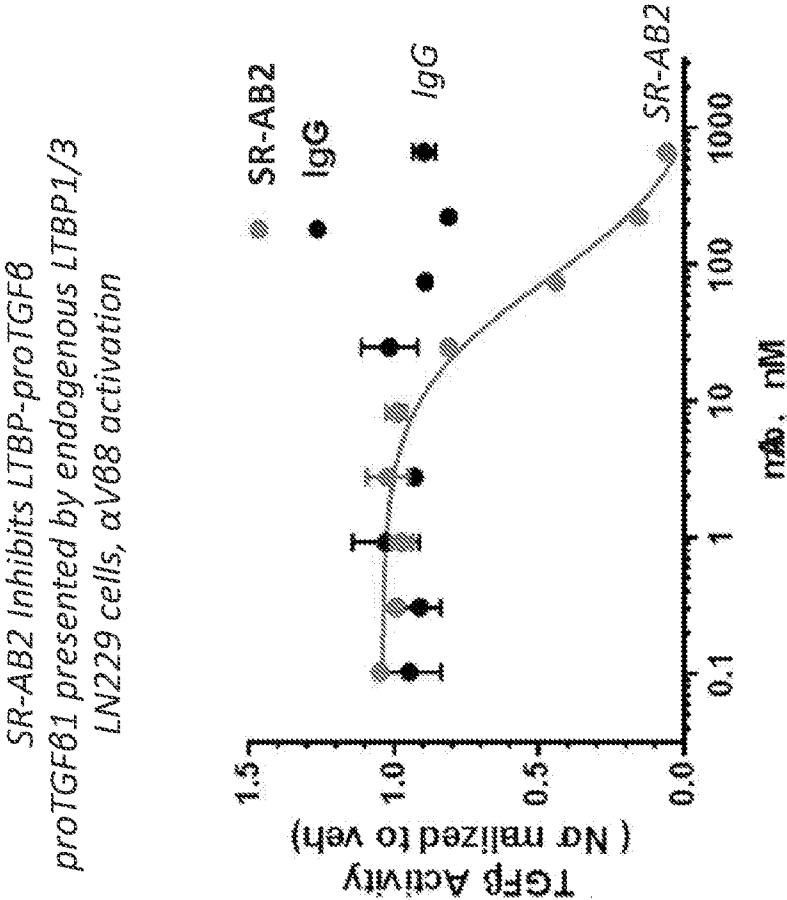


FIG. 10B: SR-AB2 Selectively Inhibits Activation of Matrix-Associated, but not GARP-Associated, proTGFβ1

*SR-AB2 Does Not Inhibit GARP-proTGFβ
proTGFβ1 presented by overexpressed GARP
LN229 cells, αVβ8 activation*

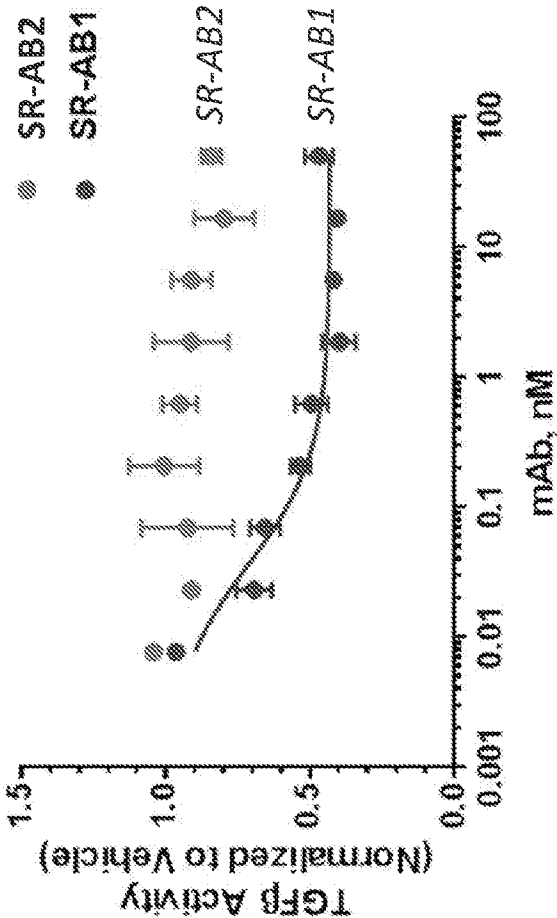
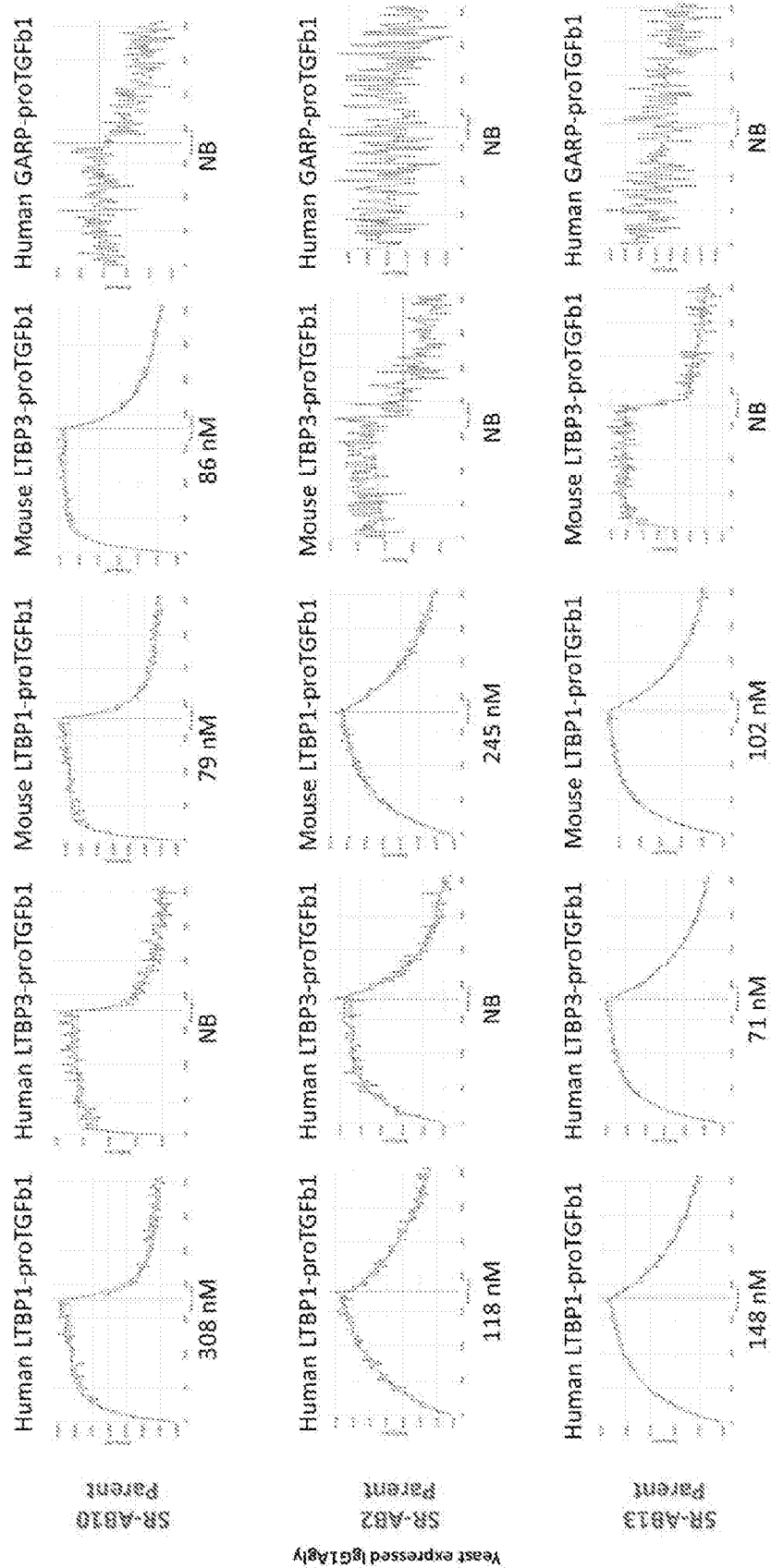


FIG. 11: In Vitro Binding Profiles of LTBP-Selective Antibodies



Initial Optimization (i.e., CDR H1/H2 diversification) of LTBP-Specific Antibodies SR-AB10 and SR-AB13 Improves Potency

FIG. 12A: Endogenous LTBP Assay

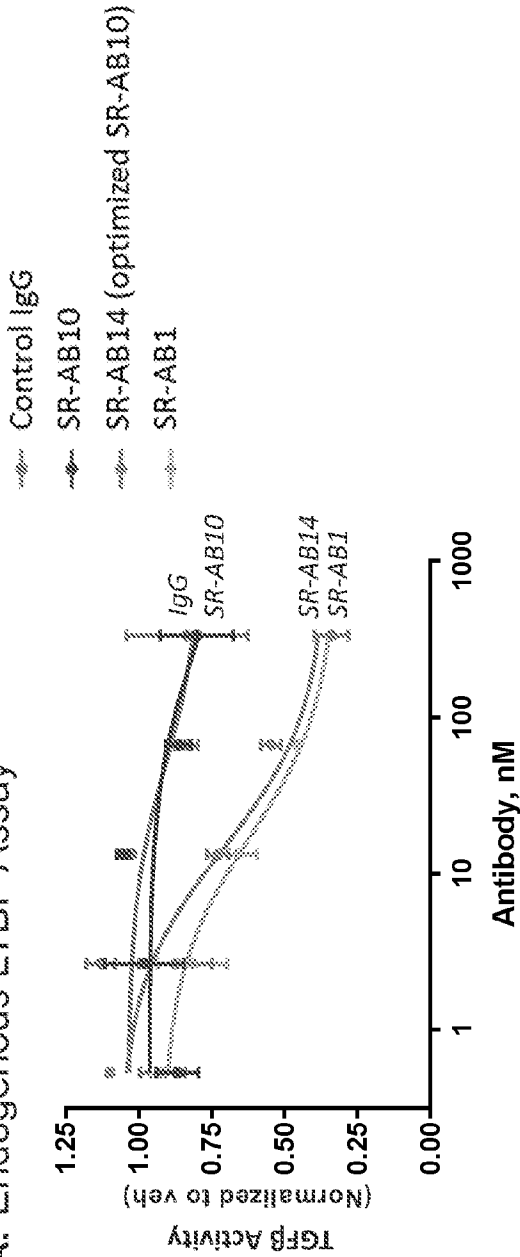
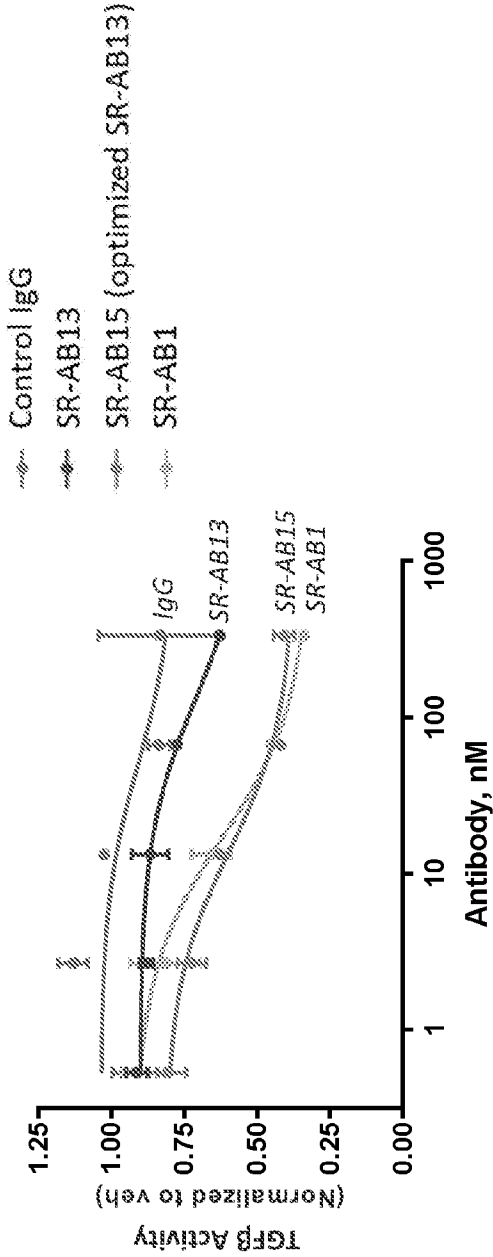


FIG. 12B: Overexpressed LTBP Assay



Second Round of Optimization (i.e., CDR-H3 mutagenesis) Further Improves Potency of AB10-related antibodies

FIG. 13A

Endogenous LTBP-proTGFβ1

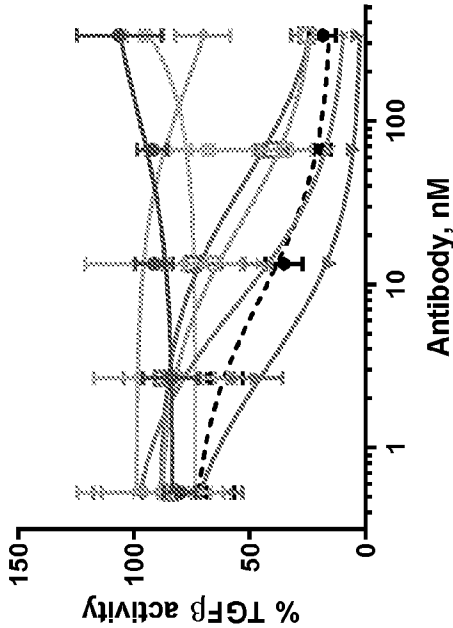
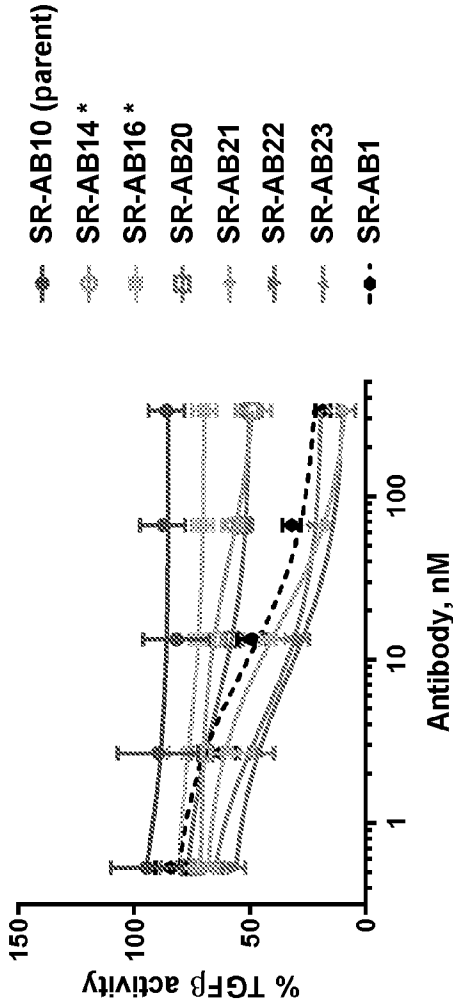


FIG. 13B

Overexpressed Murine LTBP1-proTGFβ1



* = cycle 1 optimized antibodies

Second Round of Optimization (i.e., CDR-H3 mutagenesis) Further Improves Potency of AB13-related antibodies

FIG. 14A

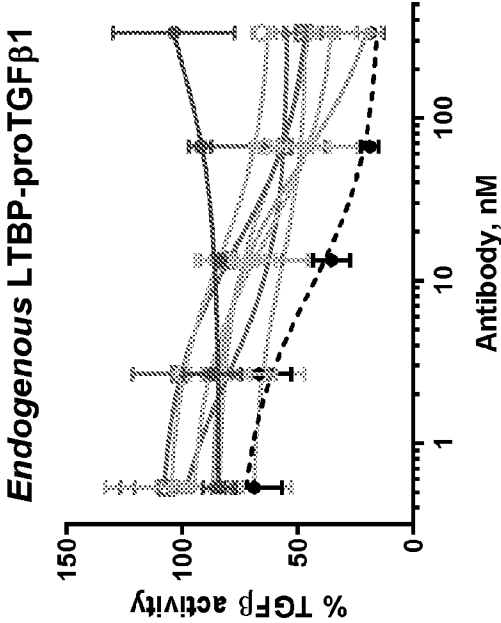
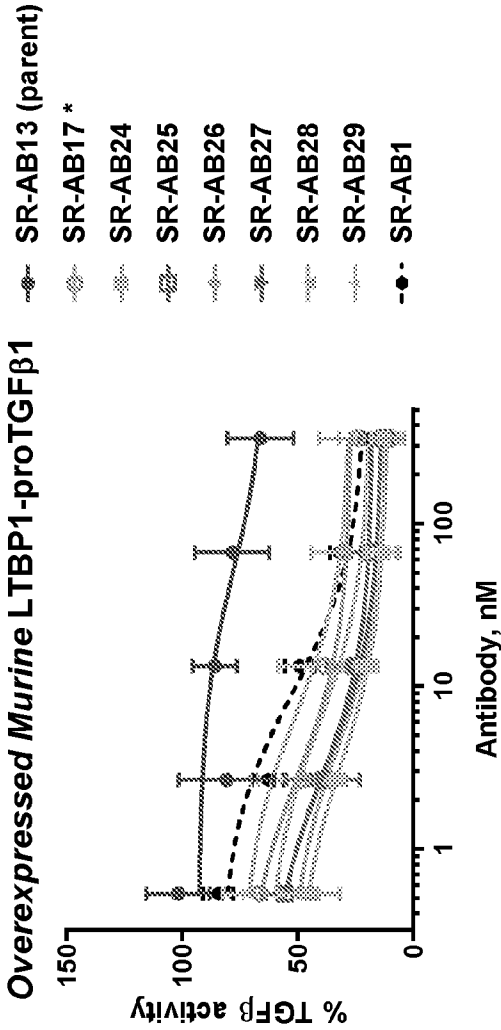


FIG. 14B



- SR-AB13 (parent)
- SR-AB17 *
- SR-AB24
- SR-AB25
- SR-AB26
- SR-AB27
- SR-AB28
- SR-AB29
- SR-AB1

* = cycle 1 optimized antibody

FIG. 15: Affinity matured antibodies show specific binding to the LTBP-proTGFβ1 complex

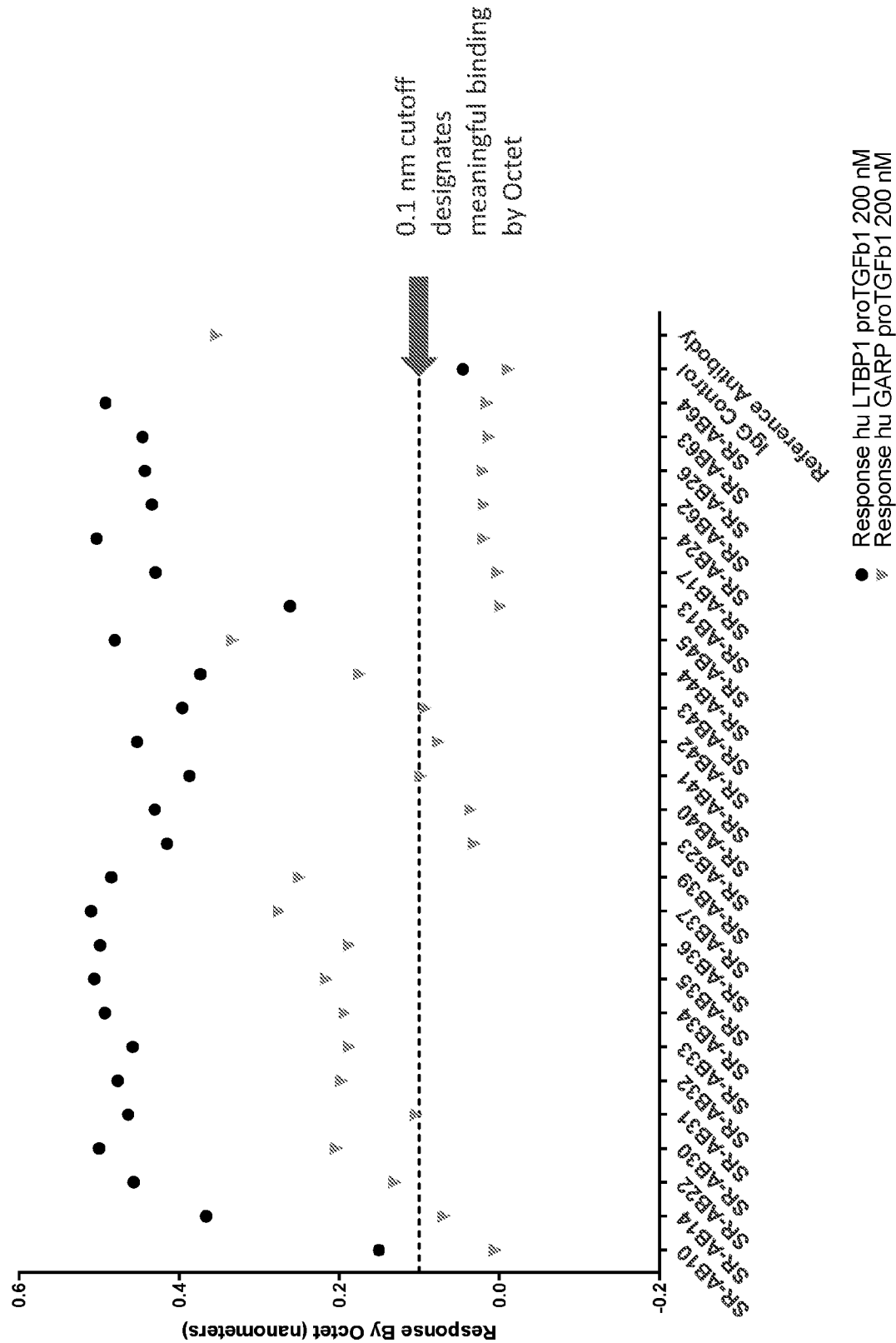


FIG. 16: Functional Activity of LTBP Complex Specific Antibodies

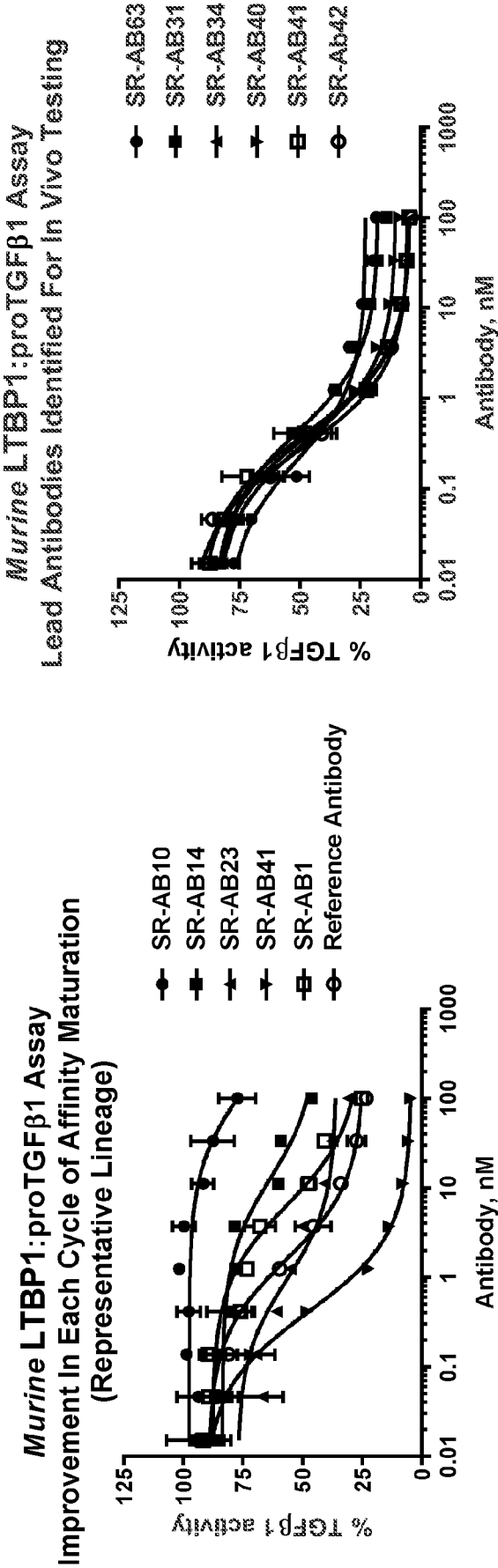


FIG. 17

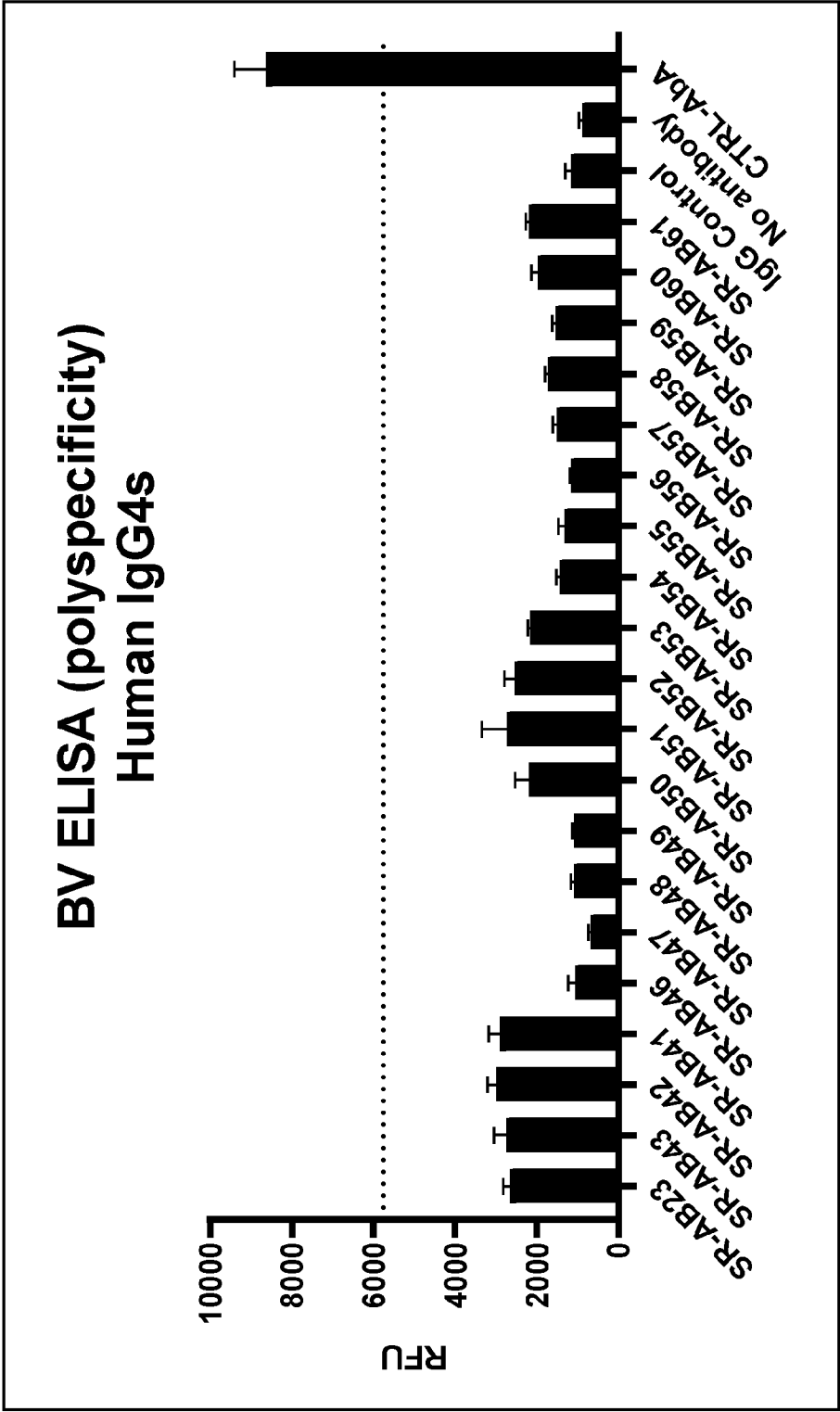


FIG. 18

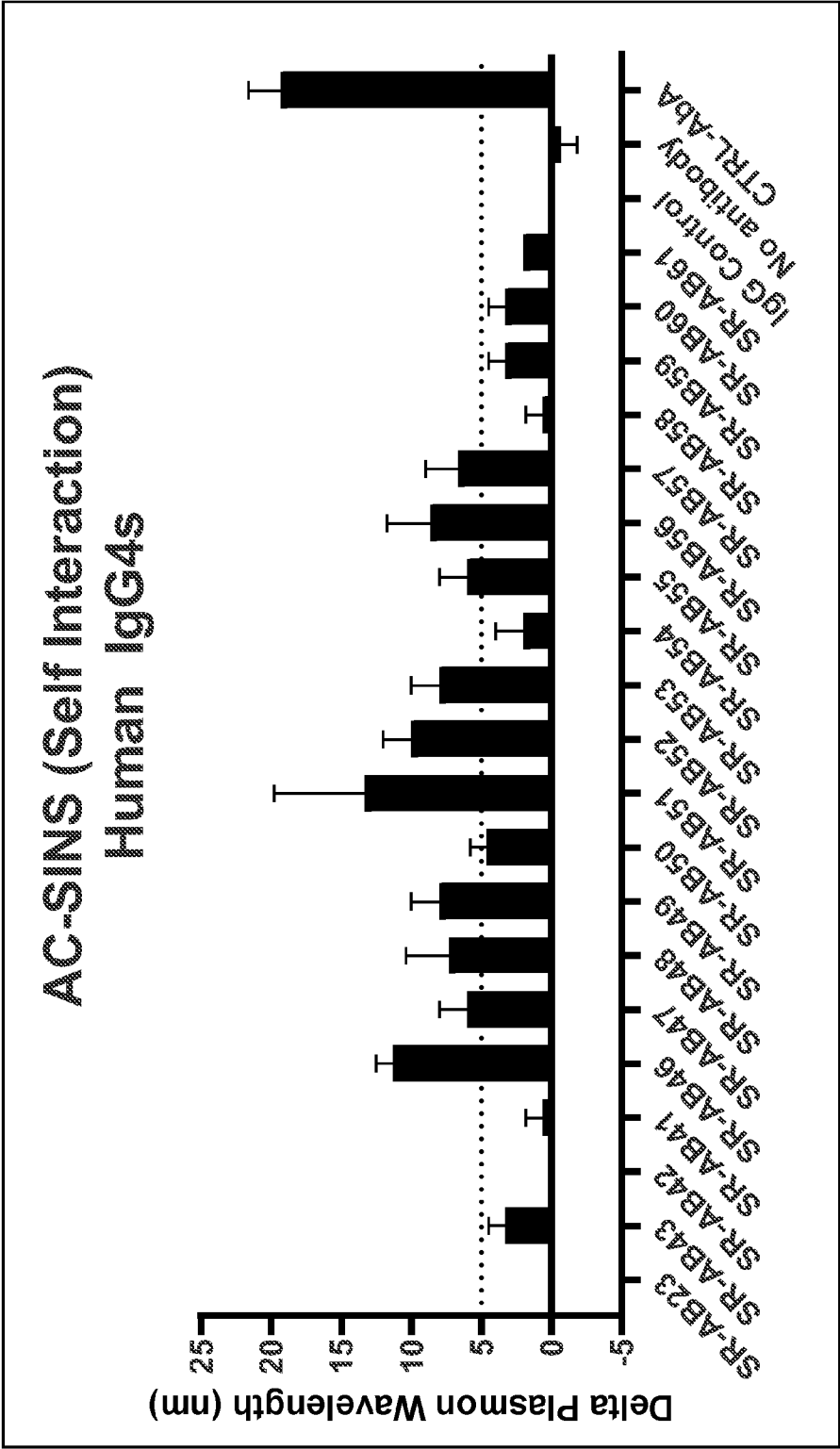


FIG. 19: LTBP Specific Antibodies Reduce Hydroxyproline Content in Mouse CDHFD Liver Tissue

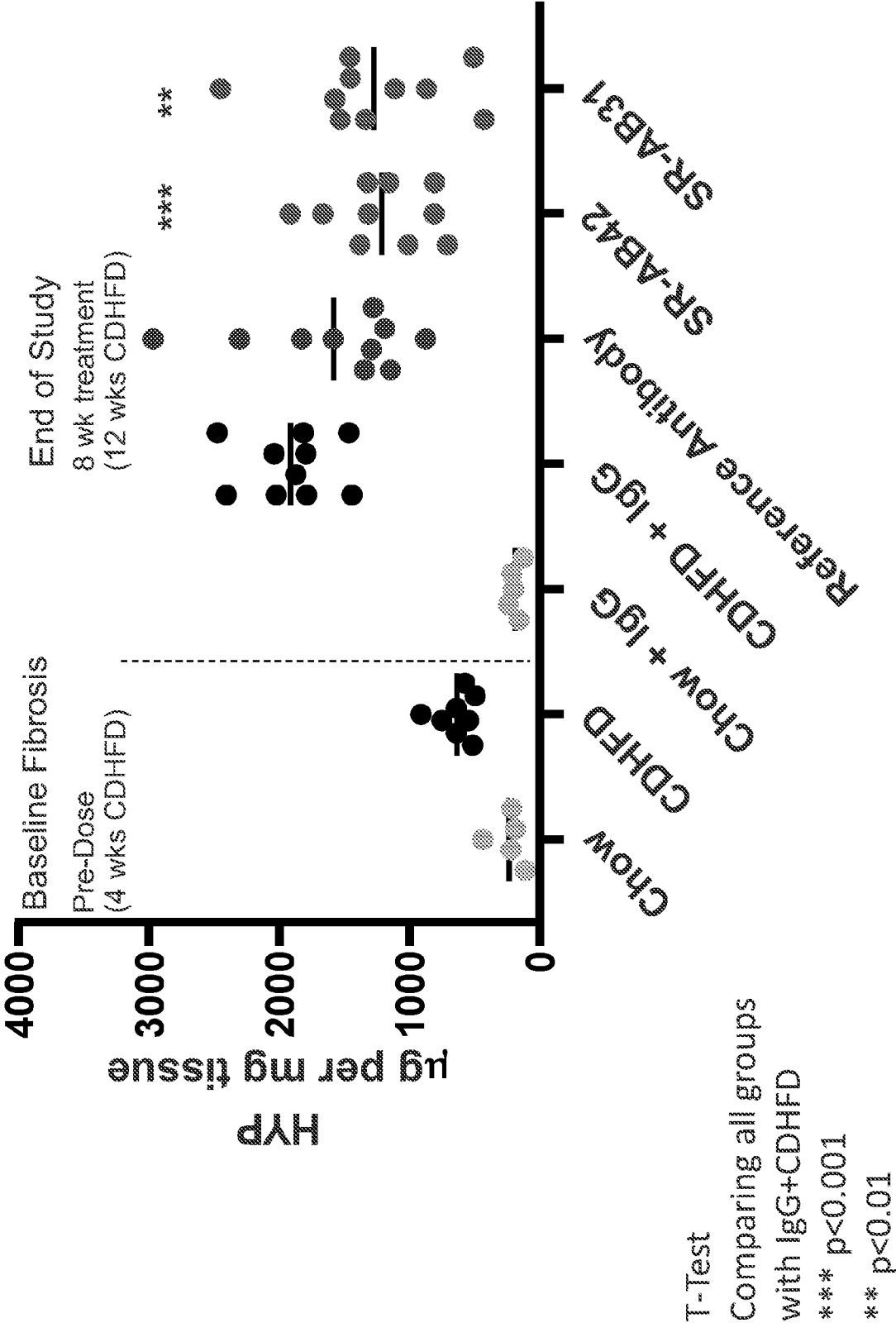
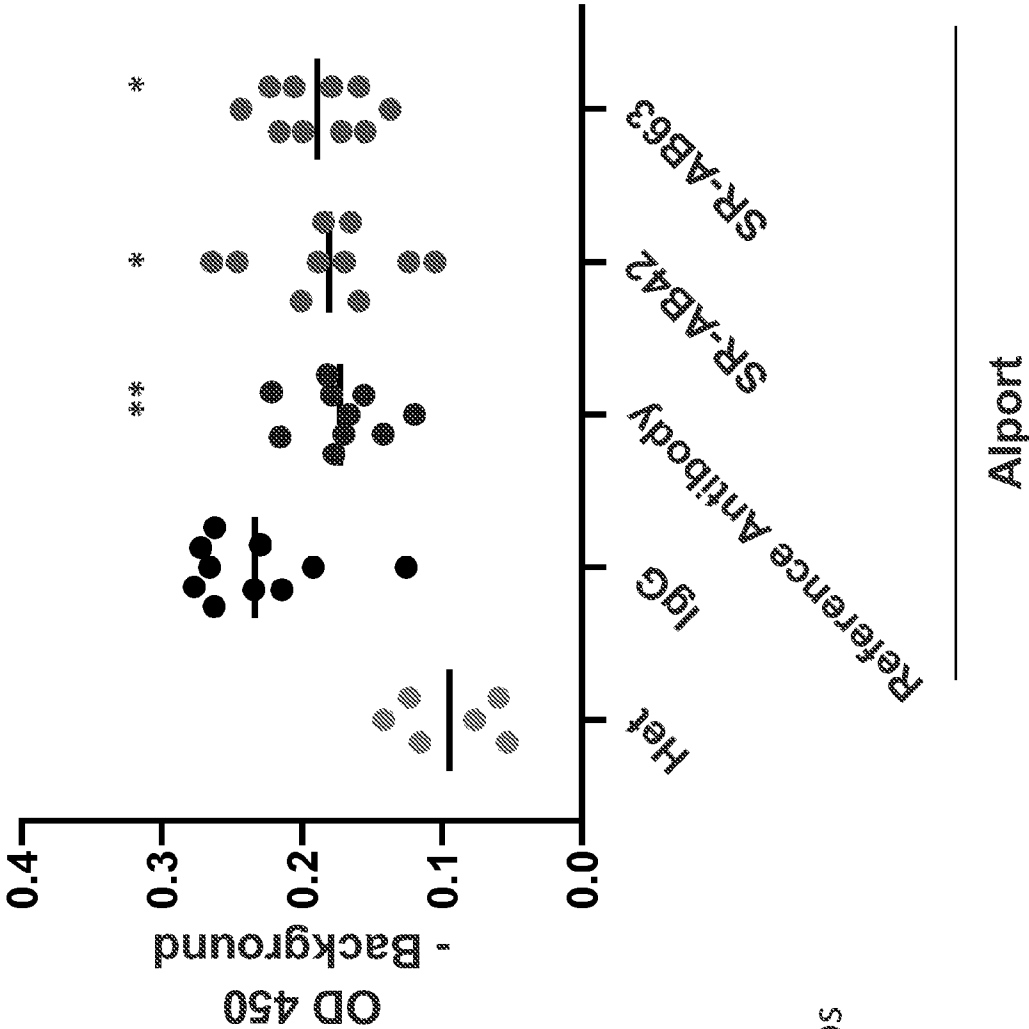


FIG. 20A: Ratio of pSmad2/3:tSmad2/3 30mg/kg dose

Ratio of pSmad2/3:tSmad2/3



T-Test
Comparing all groups
with IgG
* p<0.05
** p<0.01

FIG. 20C

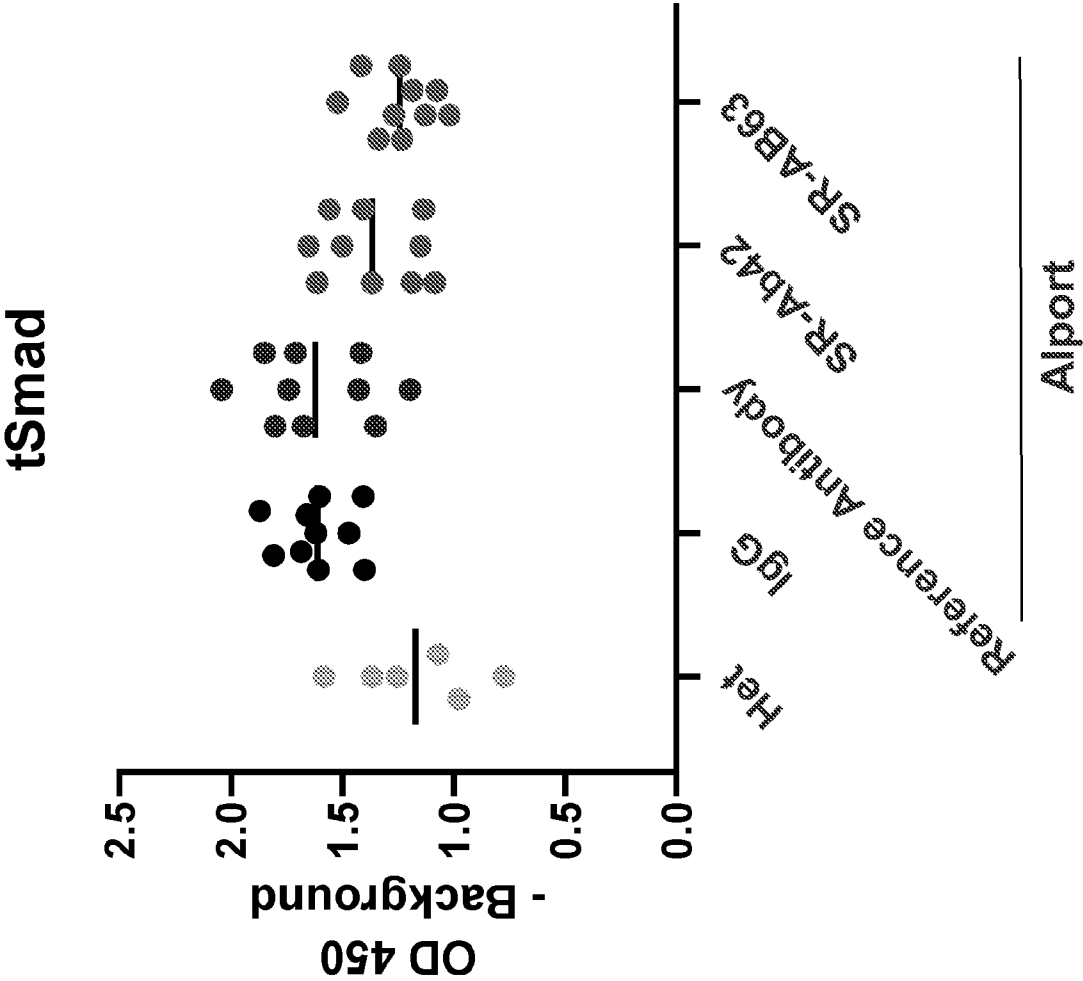


FIG. 22
TGFβ3-selective inhibitor exacerbates fibrosis and suppresses anti-fibrotic effects of TGFβ1-selective inhibitor in mouse CDHFD model

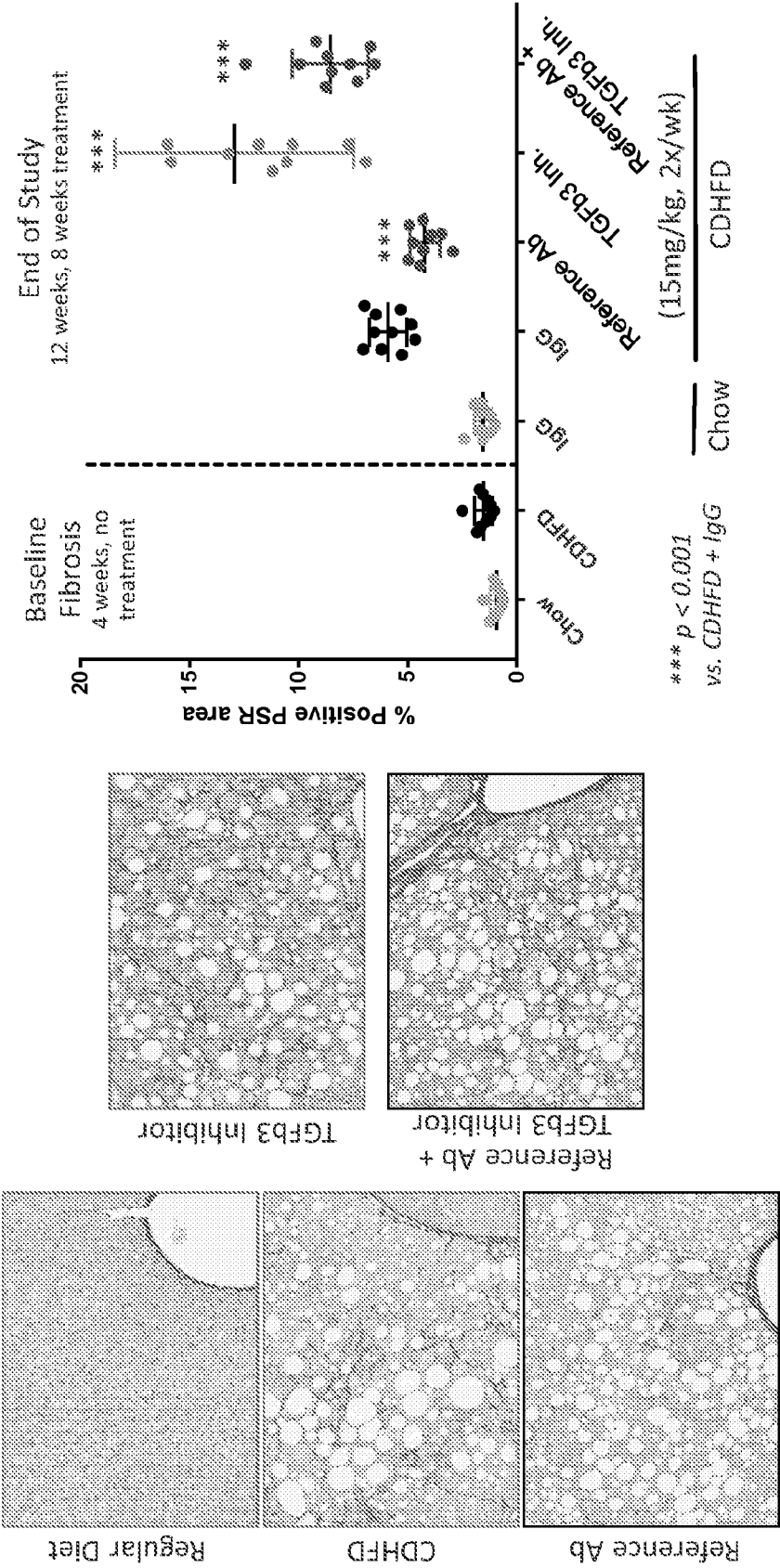
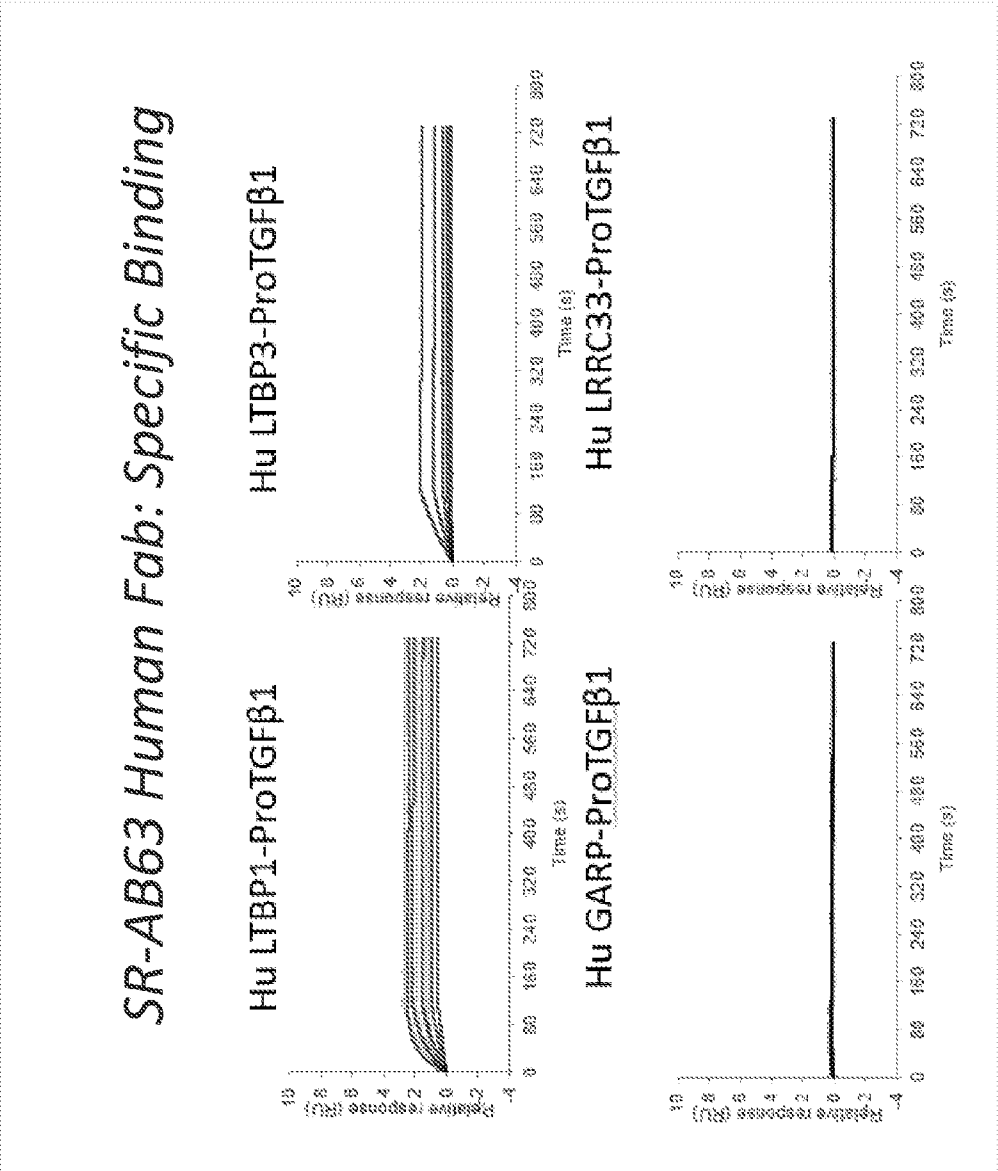


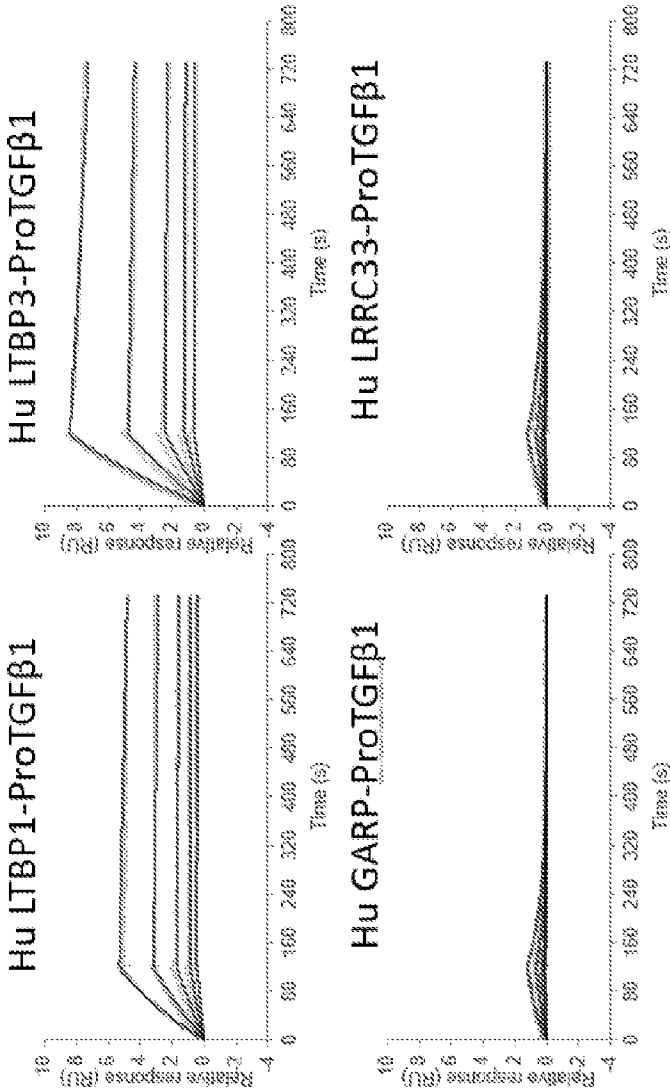
FIG. 23: LTBP Antibodies Are Highly Specific and Have Picomolar Monovalent Affinities



LTBP-SR-AB63 Hu Fab	KD (nM)
Hu LTBP1-ProTGFβ1	0.03
Hu LTBP3-ProTGFβ1	0.1
Hu GARP-ProTGFβ1	Not detectable
Hu LRRC33-ProTGFβ1	Not detectable

FIG. 24: LTBP Antibodies Are Highly Specific and Have Picomolar Monovalent Affinities

SR-AB42 Human Fab: Specific Binding



LTBP-SR-AB42 Hu Fab	KD (nM)
Hu LTBP1-ProTGFβ1	0.38
Hu LTBP3-ProTGFβ1	0.57
Hu GARP-ProTGFβ1	144
Hu LRRC33-ProTGFβ1	134