Figure S1

A SNU5
(*MET amplification*)

B

IgG4 Control | METxMET | Parental Ab1 | Parental Ab2

FL3-PI

FL1-AnnexinV

C EBC1

- IgG4 Control
- METxMET
- Parental Ab1
- Parental Ab2

D NCI-H358
(*MET wt*)

- IgG4 Control
- METxMET
- Parental Ab1
- Parental Ab2

E NHBE
(*MET wt*)

F

MET

Tubulin   SNU5
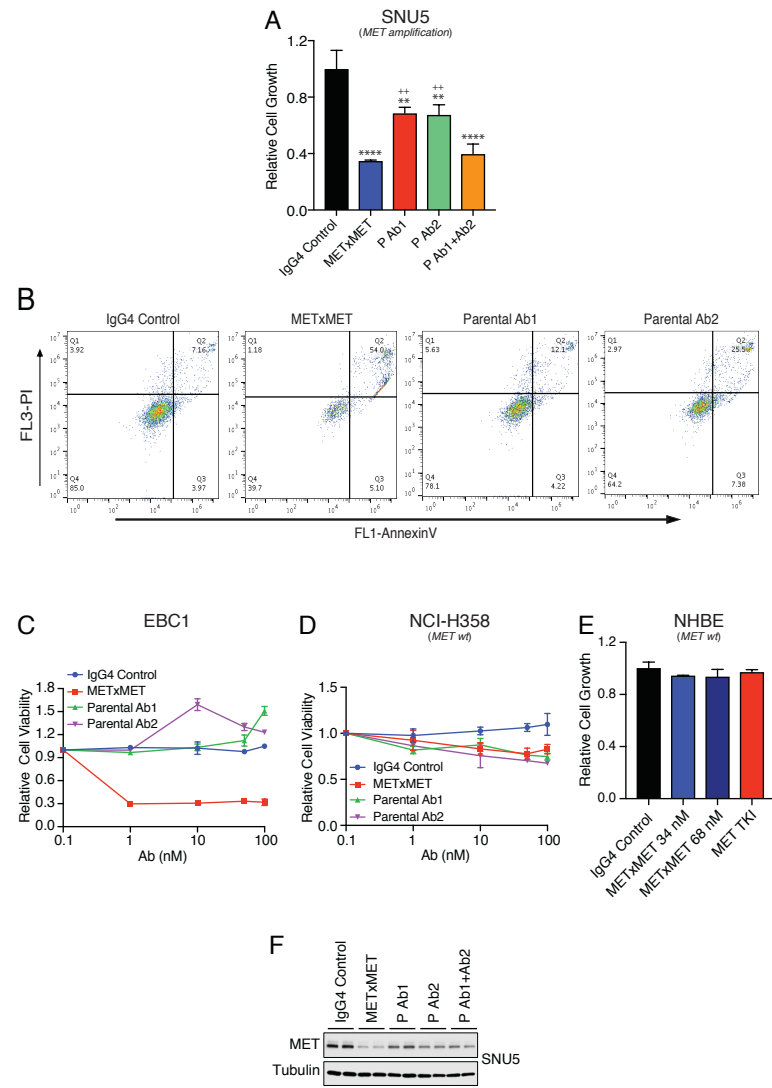
Figure S2

A hMET (monomeric)

B hMET (dimeric)
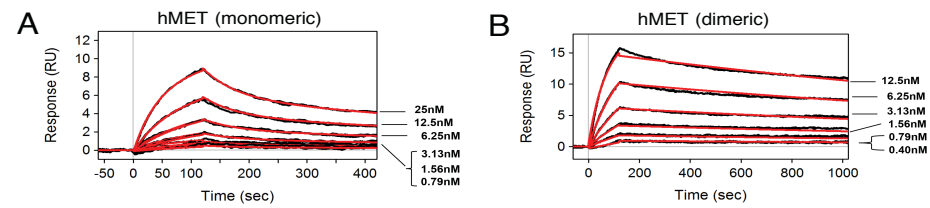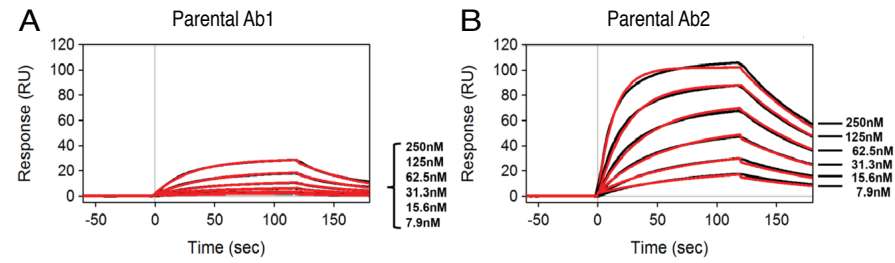
Protein injected over surface-captured METxMET	Kinetic Binding Parameters							
	k_a1 $(M^{-1}s^{-1})$	k_d1 (s^{-1})	K_D1 (M)	$t_{1/2}1$ (min)	k_a2 $(M^{-1}s^{-1})$	k_d2 (s^{-1})	K_D2 (M)	$t_{1/2}2$ (min)
hMET (monomeric)	6.70×10^5	1.76×10^{-2}	2.63×10^{-8}	0.7	4.45×10^5	1.17×10^{-3}	2.63×10^{-9}	9.9
hMET (dimeric)	1.11×10^6	3.59×10^{-4}	3.22×10^{-10}	32.2	NA	NA	NA	NA

ka, association rate constant; kd, dissociation rate constant; KD, equilibrium dissociation constant; t½, dissociative half-life; NA, not applicable because kinetic parameters were determined using a 1:1 binding model. Due to biphasic dissociation of monomeric MET proteins, the kinetic parameters were determined using a heterogeneous ligand binding model.

Figure S3

A Parental Ab1

B Parental Ab2

Kinetic Binding Parameters

	Protein injected over surface captured parental antibodies	k_a (M^{-1}s^{-1})	k_d (s^{-1})	K_D (M)	$t_{1/2}$ (min)
Parental Ab1	hMET (monomeric)	6.36×10^4	1.61×10^{-2}	2.53×10^{-7}	0.7
Parental Ab2	hMET (monomeric)	2.56×10^5	1.03×10^{-2}	4.01×10^{-8}	1.1

ka, association rate constant; kd, dissociation rate constant; KD, equilibrium dissociation constant; t½, dissociative half-life.
Kinetic parameters were determined using a 1:1 binding model.

Figure S4

EBC1

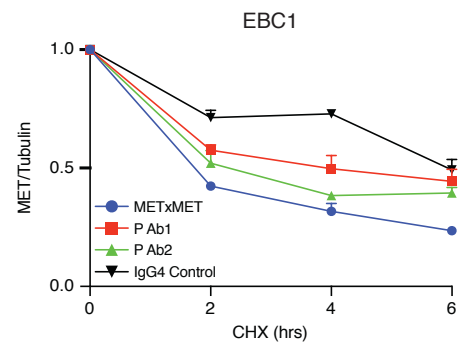MET/Tubulin

1.0

0.5

0.0

0   2   4   6

CHX (hrs)

- METxMET
- P Ab1
- P Ab2
- IgG4 Control

Figure S5

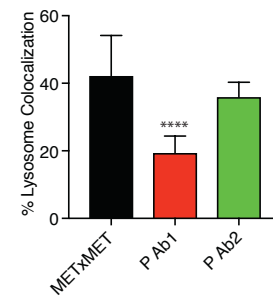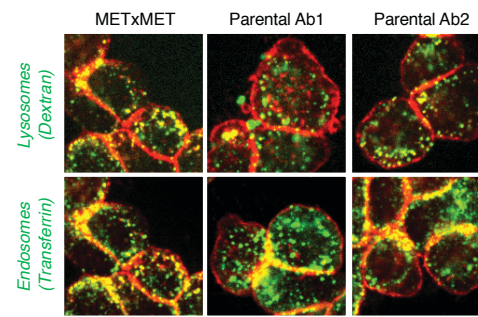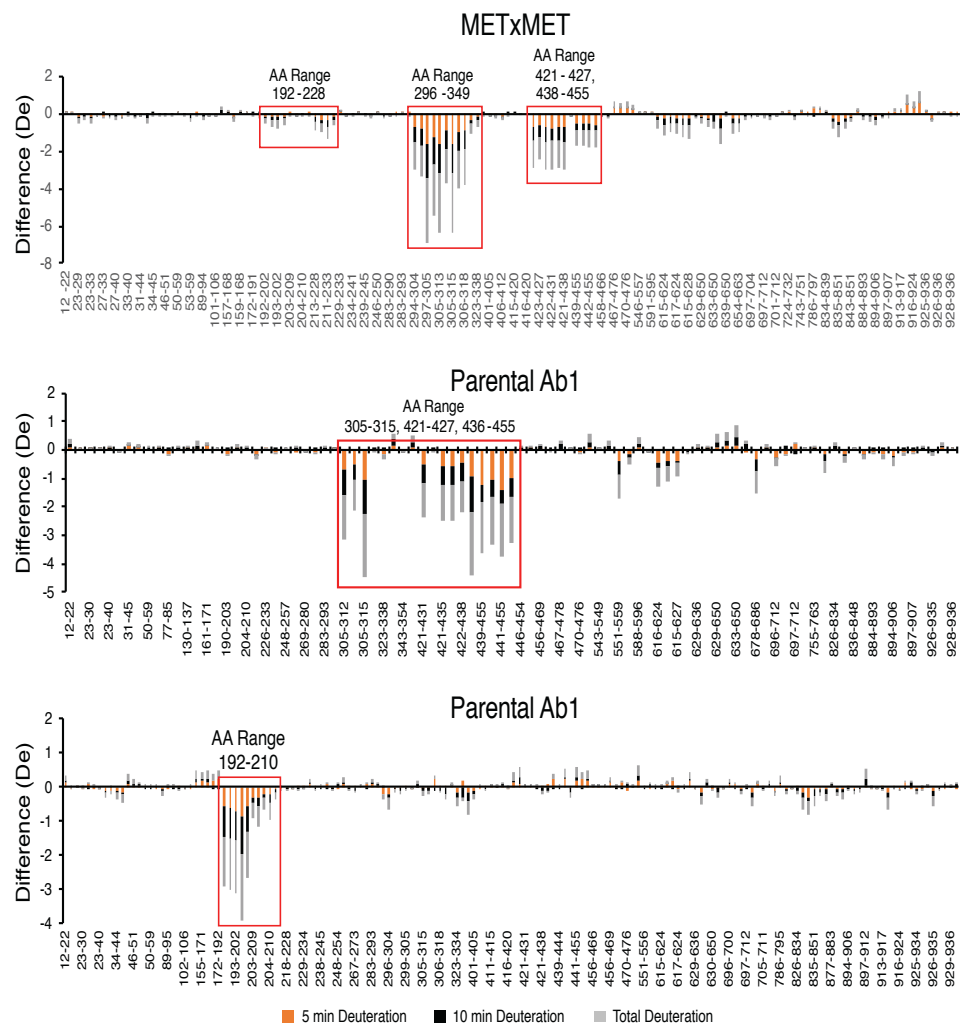|	METxMET	Parental Ab1	Parental Ab2
Lysosomes (Dextran)			
Endosomes (Transferrin)			

Figure S6

Table S1. Activation of MET-dependent gene expression by conventional antibodies

Conventional MET Ab	Luciferase activity (fold over untreated)	EC50 (M)
Ab 1	14.4	3.70E -12
Ab 2*	10.9	1.20E -10
Ab 3*	9.8	1.30E -11
Ab 4	9.8	7.70E -13
Ab 5	9.2	not sigmoid
Ab 6	7.1	2.30E -12
Ab 7	5.2	3.00E -10
Ab 8	4.8	1.80E -10
Ab 9	4.3	1.90E -10
Ab 10	3.1	4.70E -10
Ab 11	2.8	3.00E -10
Ab 12	2.8	4.80E -10
Ab 13	2.7	3.90E -10
Ab 14	2.3	4.70E -11
Ab 15	1.8	1.20E -09
Ab 16	1.7	1.40E -11
Ab 17	1.6	4.40E -10
Ab 18	1.4	1.90E -09
Ab 19	1.2	not sigmoid

Luciferase reporter gene expression (driven by serum response element) was
determined in HEK293 cells
* Parental antibodies selected for generation of the METxMET biparatopic antibody

Table S2. The MET biparatopic antibody binds to non-overlapping epitopes of human MET

First Antibody Injected (Pre-bound Ab)	First Antibody Binding Signal (RU)	Second Antibody Injected	Binding Signal (RU)	Percent Blocking
METxMET	150.9±0.2	METxMET	0.6	100.0
		Parental Ab1	4.7	94.7
		Parental Ab2	-8.3	113.7
		Control Ab	-12.4	NC
Parental Ab1	115.4±2.0	METxMET	82.3	27.2
		Parental Ab1	0.7	100.0
		Parental Ab2	44.2	25.2
		Control Ab	-24.4	NC
Parental Ab2	85.9±0.4	METxMET	90.0	20.4
		Parental Ab1	70.7	7.8
		Parental Ab2	-0.2	100.0
		Control Ab	-8.6	NC
IgG4 Control	2.6±2.5	METxMET	112.9	0.0
		Parental Ab1	76.6	0.0
		Parental Ab2	59.2	0.0
		Control Ab	-0.2	NC

Percent blocking was calculated by using the following formula:
% Blocking = 100 – (Binding Signal – Self-Self) / (Maximum Binding Signal – Self-Self) * 100
Where Binding Signal is defined as the response generated by the second Ab injected over pre-bound first Ab.
Self-Self is defined as the binding response when the second Ab is injected over itself pre-bound to the surface.
Maximum Binding Signal is defined as the difference between the binding signal generated by each antibody injected over pre-bound control antibody.
Abbreviations: NC, not calculated because dividing by 0 is undefined.