18th International Myeloma Workshop

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The Role of Checkpoint Inhibitor PD-1H/VISTA in Multiple Myeloma Bone Disease

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Disclosure

S. Lentzsch reports Caelum Biosciences equity ownership and membership on Caelum Bioscience's board of directors or advisory committees; consultancy for Janssen, Takeda, GSK, Antengene, Adaptive and Sorrento and received research funding from Karyopharm and Sanofi.

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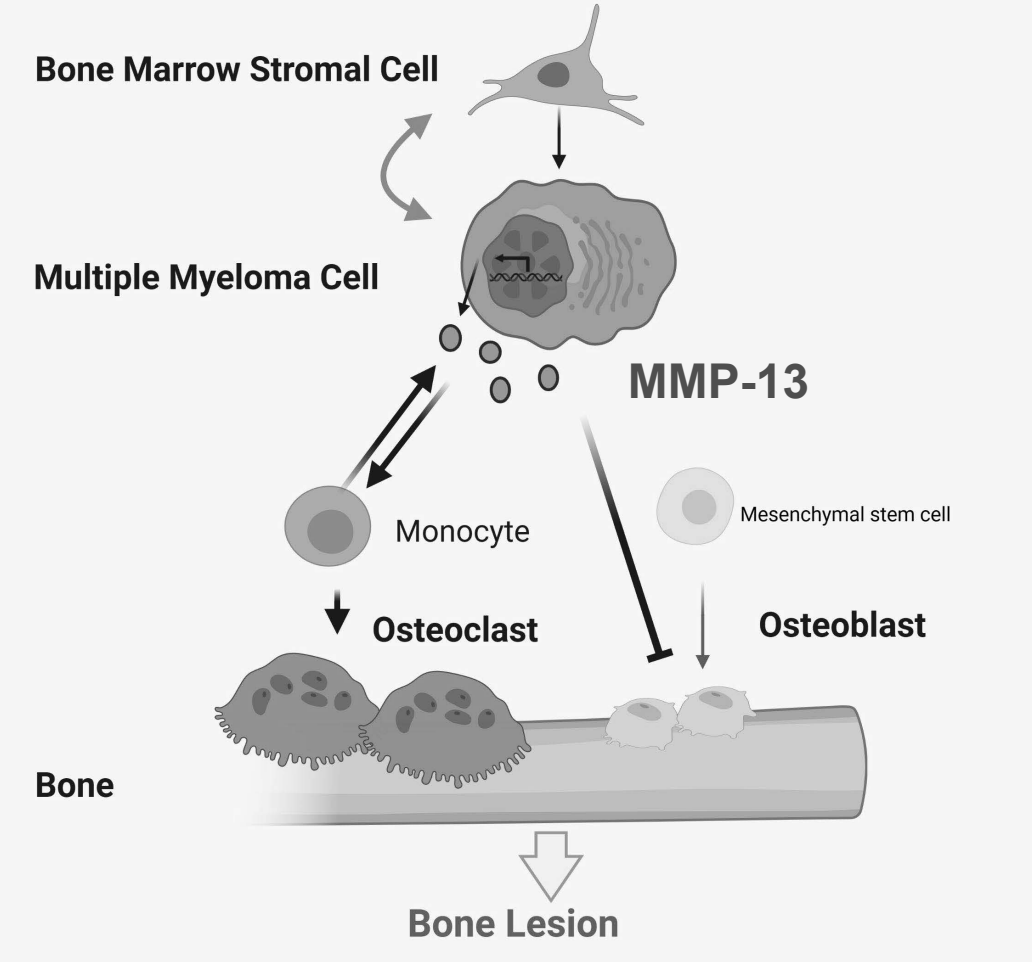
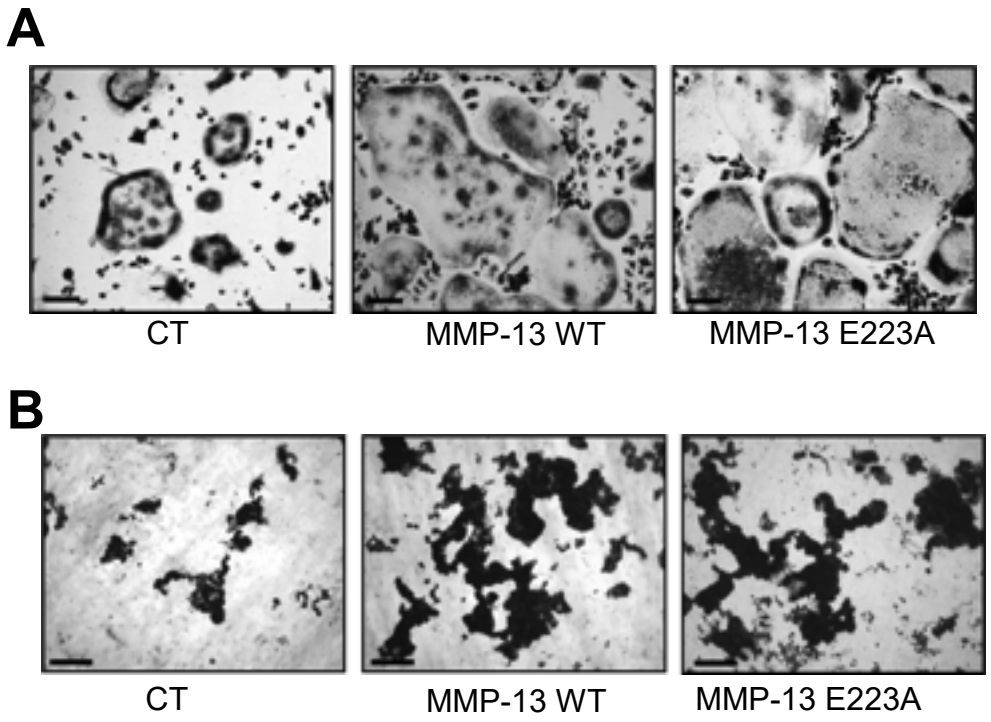
The remaining authors declare no competing financial interests.

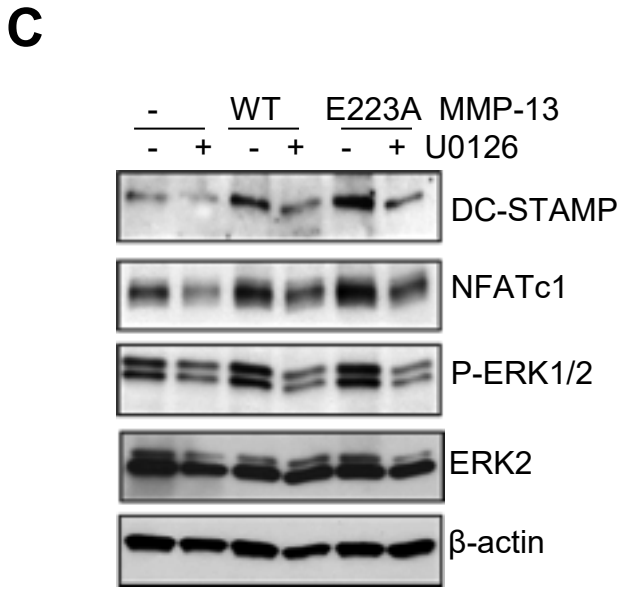
Multiple Myeloma Bone Disease



Adapted from Palumo, A. *et al*, *NEJM.* 2011

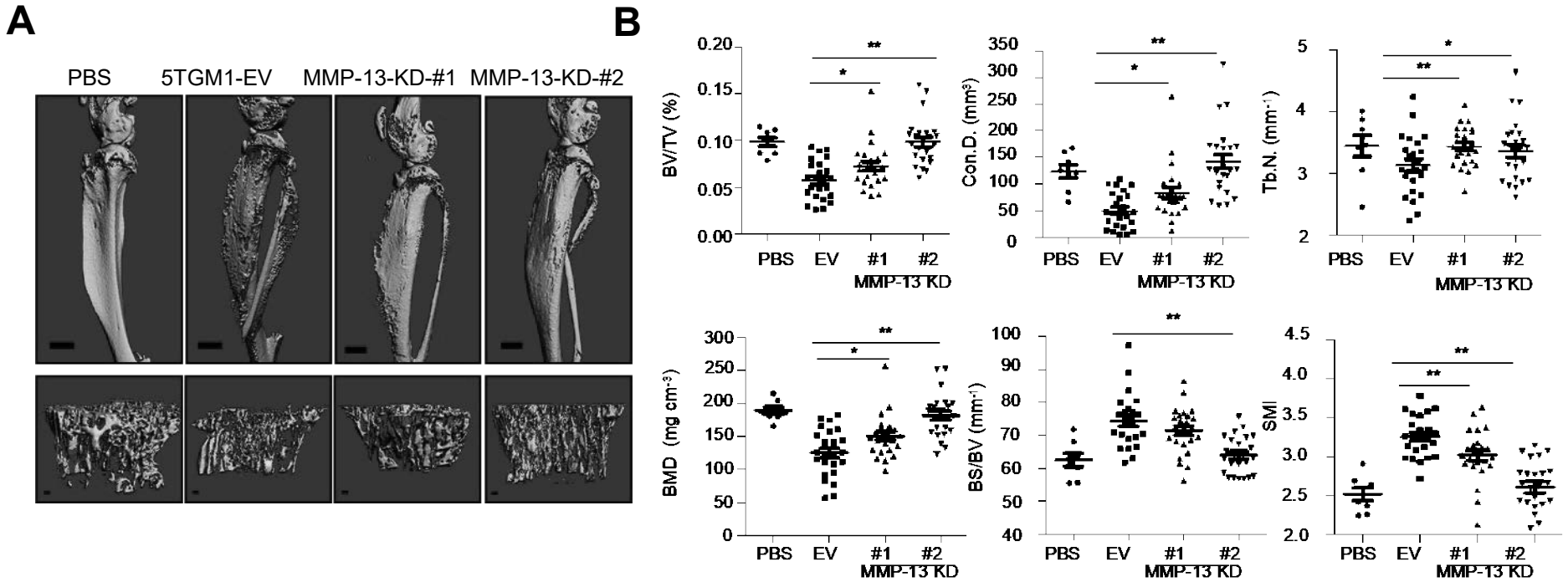
MMP-13 induces osteoclast fusion





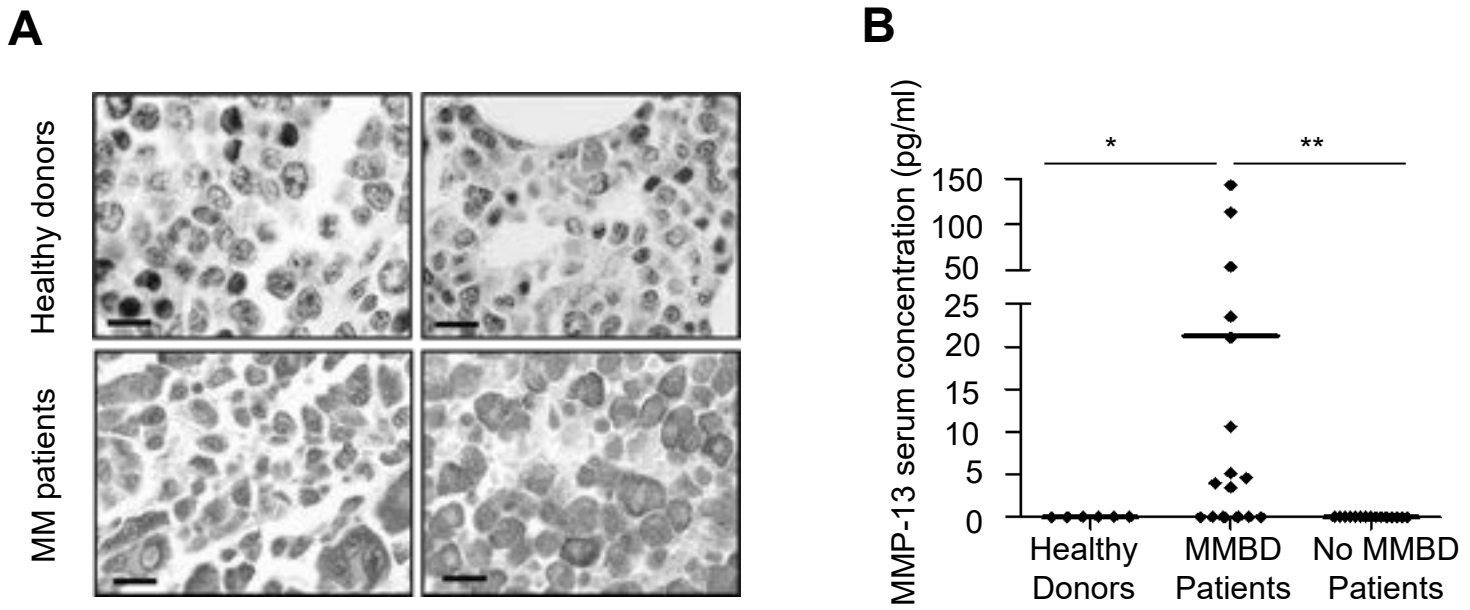
Fu, J. *et al. J Clin Invest*. 2016

MMP-13 KD inhibits MM induced lytic bone lesion



Fu, J. *et al. J Clin Invest*. 2016

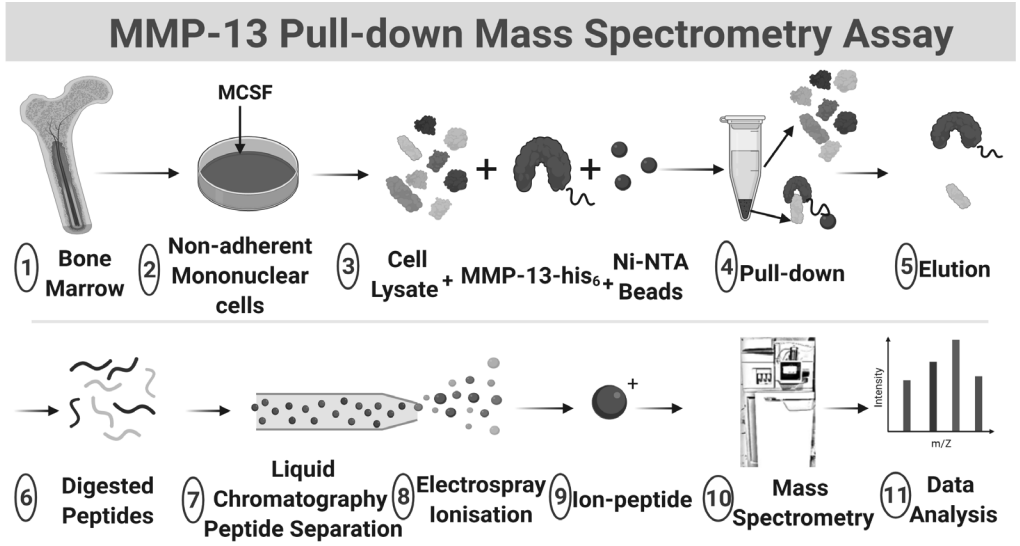
MMP-13 is highly expressed in MM and correlates with bone disease



Fu, J. *et al. J Clin Invest*. 2016

Screening of MMP-13 binding protein

A

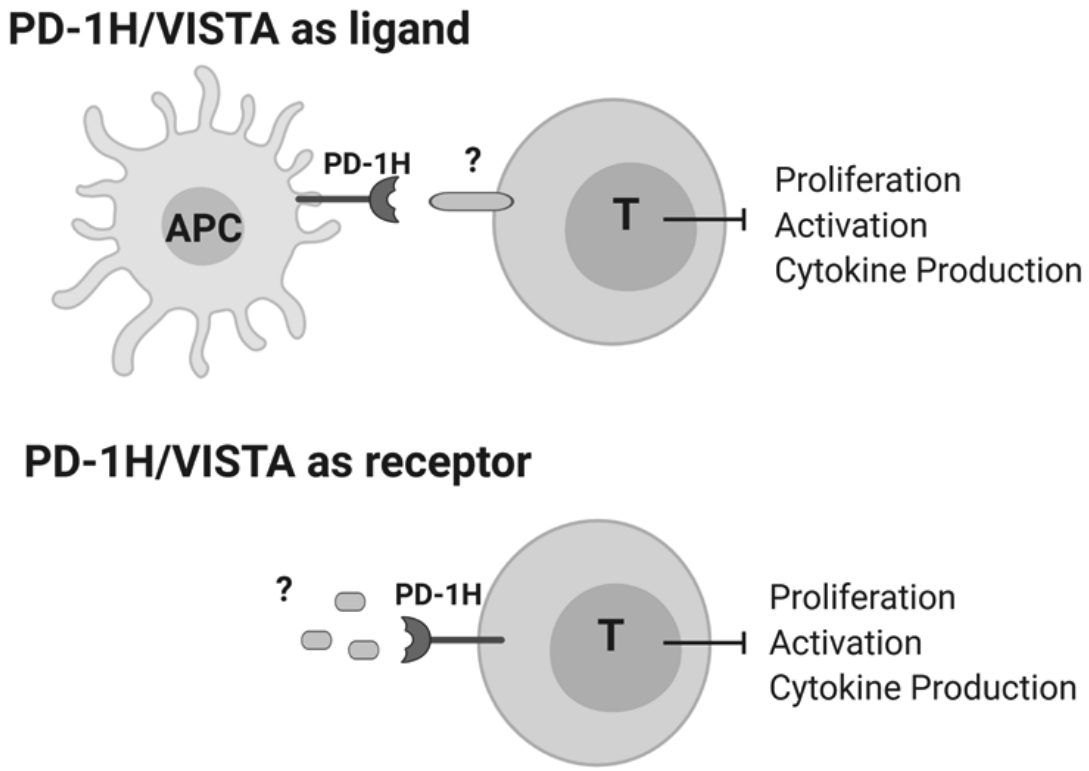


B

UniProt Accession	Uniprot ID	Protein	Peptide Count	Ratio [MMP-13 / Control]	P-Value
CUSTOMSEQ001	CUSTOMSEQ001	**Recombinant Protein Human pro-MMP-13**	28	24.0	0
Q9D659	VISTA_MOUSE	**PD-1H / VISTA**	3	29.9	0
Q8K1X4	NCKPL_MOUSE	NCK associated protein 1 like	2	5.73	1.3E-04
P33435	MMP13_MOUSE	Collagenase 3	2	3.16	2.4E-11
O70439	STX7_MOUSE	Syntaxin-7	2	3.09	7.1E-09
P58252	EF2_MOUSE	Elongation factor 2	4	2.62	4.0E-02
P47757	CAPZB_MOUSE	F-actin-capping protein subunit beta	2	2.47	1.0E-03
Q61093	CY24B_MOUSE	Cytochrome b-245 heavy chain	2	2.39	8.2E-11
B8JJC8	B8JJC8_MOUSE	Transcriptional enhancer factor TEF-5	2	2.26	1.3E-06
O08692	NGP_MOUSE	Myeloid bactenecin (F1)	6	2.21	2.1E-05
Q9JJZ2	TBA8_MOUSE	Tubulin alpha-8 chain	2	2.15	2.2E-06
P17751	TPIS_MOUSE	Triosephosphate isomerase	8	2.04	4.0E-08
P63101	1433Z_MOUSE	14-3-3 protein zeta/delta	2	1.69	9.0E-03
P63260	ACTG_MOUSE	Actin, cytoplasmic 2	3	1.69	8.7E-04
P08905	LYZ2_MOUSE	Lysozyme C-2	2	1.66	2.1E-05
P49290	PERE_MOUSE	Eosinophil peroxidase	3	1.60	9.0E-03
Q8R2S8	CD177_MOUSE	CD177 antigen	2	1.51	1.0E-06

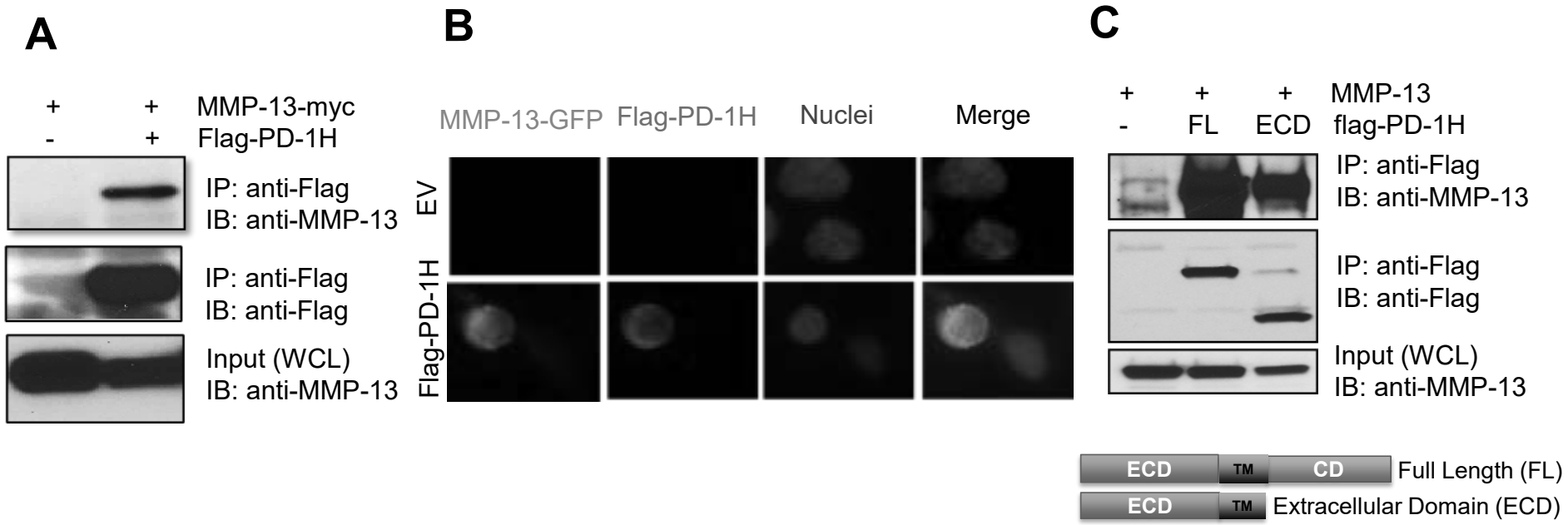
Lentzsch Lab, unpublished data

PD-1H/VISTA checkpoint inhibitor



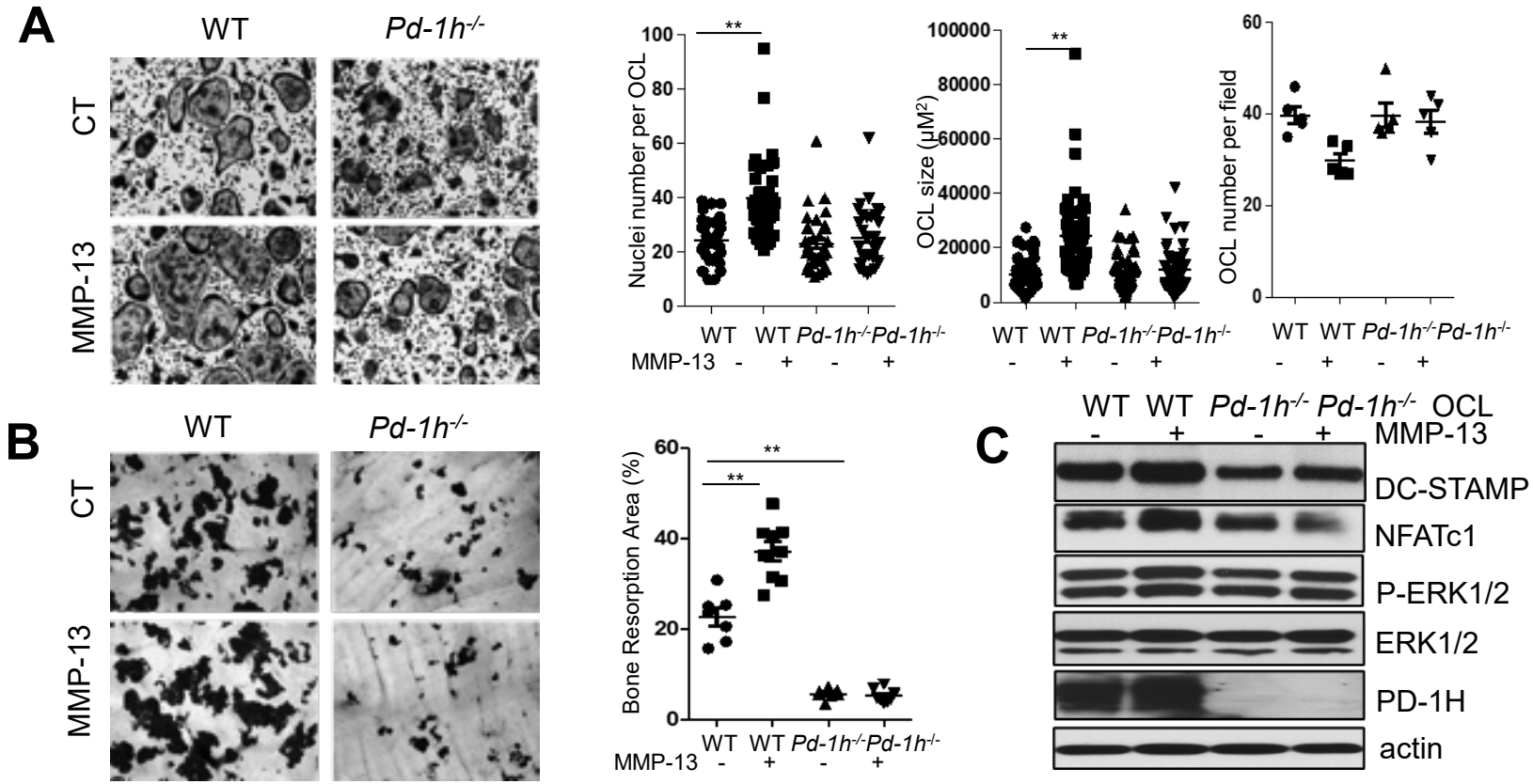
Adapted from Nowak. E, *et al*, *Immunol Rev.* 2017

PD-1H mediates MMP-13 cellular binding



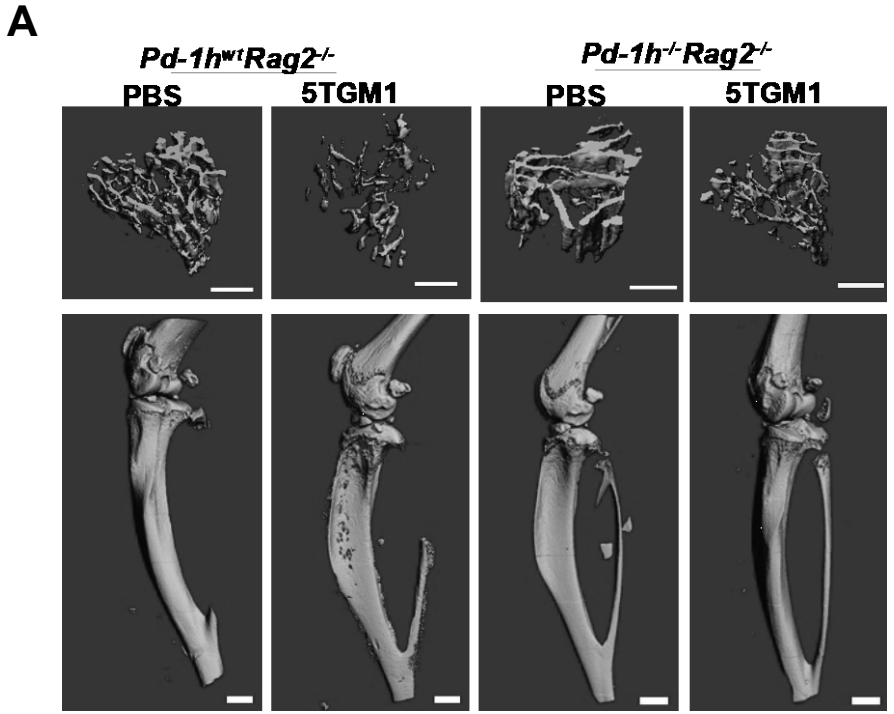
Lentzsch Lab, unpublished data

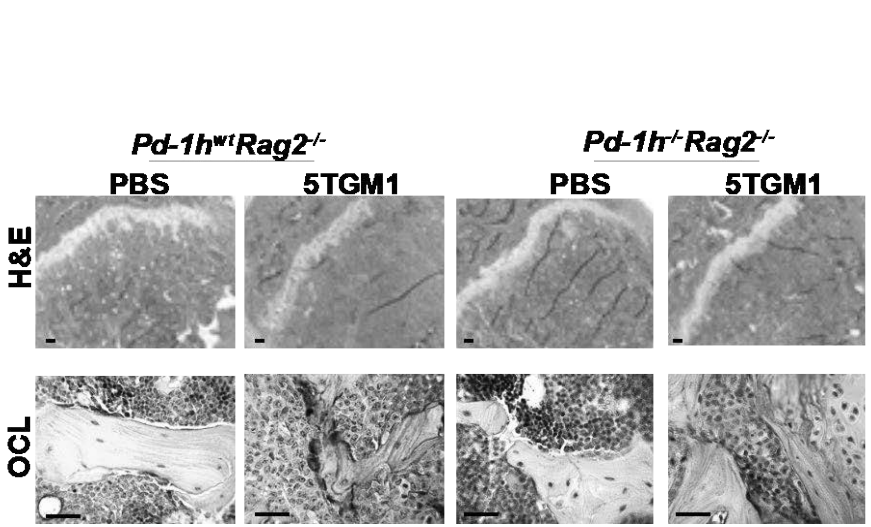
Pd-1h$^{-/-}$ impairs MMP-13 induced OCL activation



Lentzsch Lab, unpublished data

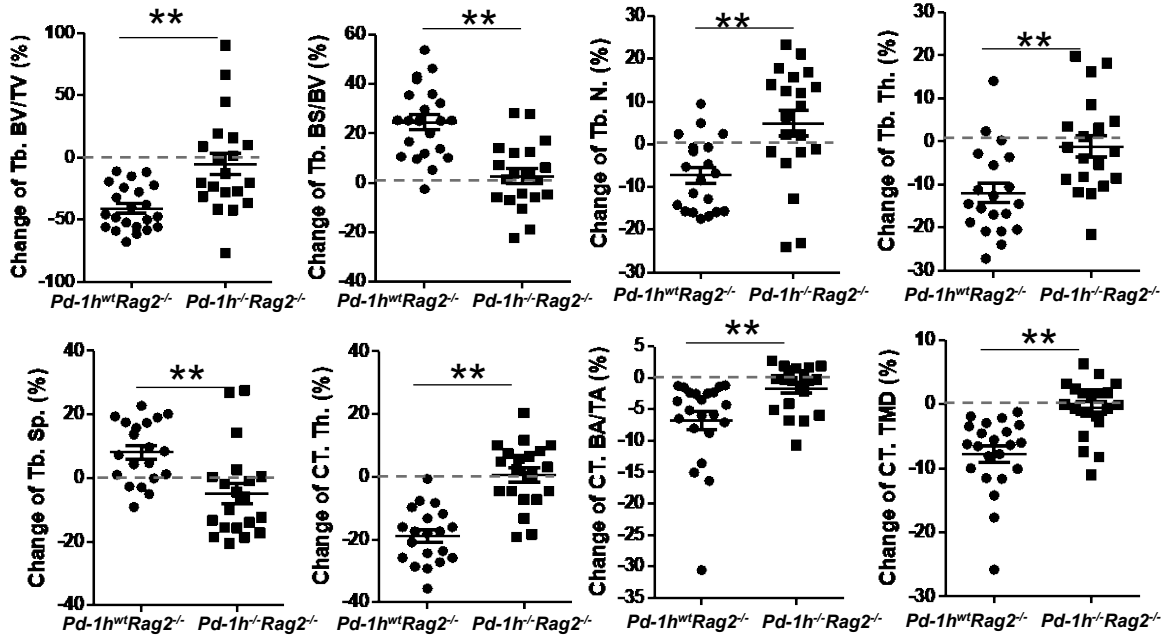
Pd-1h$^{-/-}$ impairs MM induced bone lesion in mice





Lentzsch Lab, unpublished data

Pd-1h$^{-/-}$ impairs MM induced bone lesion in mice



5TGM1 MM induced relative change

	Tb. [BV/TV]	Tb. [BS/BV]	Tb.N.	Tb.Th.	Tb.Sp.	CT. Th.	CT. [BA/TA]	CT. TMD
Pd-1h^{wt}Rag2$^{-/-}$	- 40.0%	+22.2%	-7.3%	-12.1%	+8.1%	-18.9%	-7.3%	-8.2%
Pd-1h$^{-/-}$Rag2$^{-/-}$	-12.5%	+5.5%	-0.6%	-4.2%	+0.6%	-1.6%	-2.7%	-1.7%
***P*-Value**	0.0098	0.001	0.045	0.03	0.04	7.54E-06	0.035	0.0018

Lentzsch Lab, unpublished data

Conclusion

- MMP-13 is highly expressed by myeloma cells and induces osteoclast fusion and activation independently of its enzymatic activity
- PD-1H is highly expressed in osteoclast
- PD-1H binds to MMP-13, mediates MMP-13 cellular binding, and MMP-13 induced osteoclast activation
- *Pd-1h*$^{-/-}$ mice are largely resistant to MM induced bone lesion

Acknowledgement

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