Generation of FcRH5xCD28 Bispecific Antibodies Synergizing with T-Cell Engagers for Enhanced Multiple Myeloma Treatment

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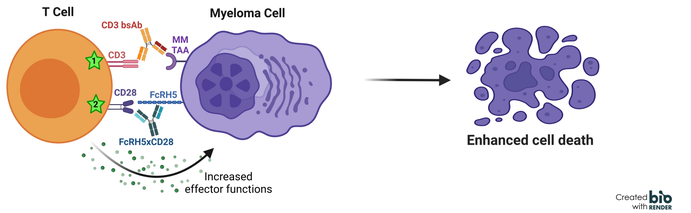
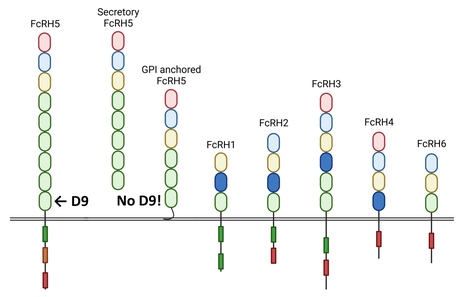
Objective

- To develop FcRH5-targeted CD28 bispecific antibodies (bsAbs) that provide selective co-stimulation of T cells, thus enhancing T cell engager (TCE) efficacy and overcoming tumor resistance mechanisms in multiple myeloma (MM) patients



FcRH5 is a highly prevalent and enriched MM marker

- FcRH5 has an extracellular domain (ECD) consisting of 9 Ig-like domains (D1 to D9)



- Importantly, MM patients display high levels of soluble FcRH5 (comprising ECD D1-8)

Soluble FcRH5 measured by ELISA

Disease	*Number of samples*	*Median (ng/ml)*	*Range (ng/ml)*
Normal	193	188	<30–600
CLL	46	958	71–6300
MM	43	481	<30–11000

Adapted from Ise et al., Leukemia (2007)

- Preferential binding to membrane-bound FcRH5 via D9 is crucial to avoid efficacy loss from the sink effect but challenging due to high similarity with other FcRH family members

INTRAMOLECULAR IDENTITY

FcRH5	D1	D2	D3	D4	D5	D6	D7	D8	D9
D1		27%	27%	26%	27%	28%	29%	27%	25%
D2	27%		26%	40%	50%	43%	/	24%	25%
D3	27%	26%		31%	30%	32%	/	32%	31%
D4	26%	40%	31%		62%	58%	46%	47%	49%
D5	27%	50%	30%	62%		70%	50%	50%	54%
D6	28%	43%	32%	58%	70%		54%	52%	54%
D7	29%	/	/	46%	50%	54%		80%	75%
D8	27%	24%	32%	47%	50%	52%	80%		77%
D9	25%	25%	31%	49%	54%	54%	75%	77%	

INTERMOLECULAR IDENTITY

FcRH5	D1	D2	D3	D5	D6
D1	38%				
D2		34%			
D3			65%		
D4				52%	52%
D5				53%	53%
D6				58%	55%
D7				81%	78%
D8				80%	84%
D9				80%	78%

Poster presented at the ASH Annual Meeting 2024 | San Diego, USA

FcRH5-dependent delivery of Signal 2 with FcRH5xCD28 bsAbs

anti-FcRH5 arm

- Binds to **FcRH5 positive multiple myeloma cells via D9**
- Allows the **clustering of CD28** at the surface of T cells
- Is cyno cross-reactive

anti-CD28 arm

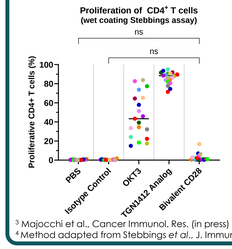
- Is an antagonist arm per se
- Turns into an **agonist arm** delivering T cell Signal 2 **after co-engaging FcRH5**
- Is cyno cross-reactive

- Designed with unbalanced arm affinity and **silenced IgG1-Fc domain**
- Truly native human bispecific IgGs built on the κλ body platform (two identical heavy chain naturally paired to one kappa and one lambda light chain)[1]
- Light chain CDRs drive specific binding to selected antigen[2]

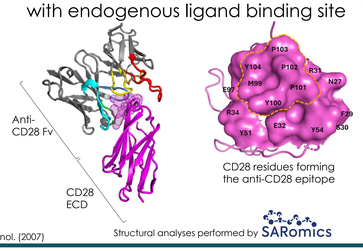
[1] Fischer *et al.*, Nat. Commun. (2015)
[2] Malinge *et al.*, mAbs (2024)

The anti-CD28 arm of FcRH5xCD28 bsAbs is not superagonist[3]

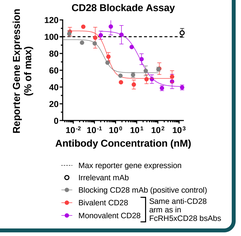
1. No superagonism[4]



2. Apical binding epitope overlapping with endogenous ligand binding site



3. Antagonistic Activity

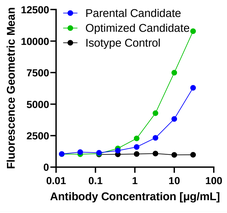


[3] Majocchi et al., Cancer Immunol. Res. (in press)
[4] Method adapted from Stebbings *et al.*, J. Immunol. (2007)

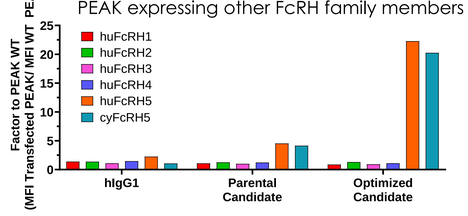
Structural analyses performed by SAROmics

FcRH5xCD28 bsAbs are FcRH5 specific and cyno cross-reactive

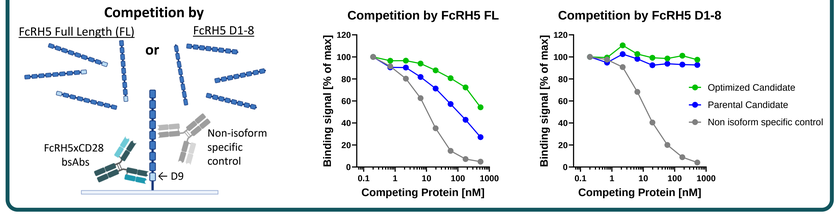
1. Dose-dependent binding to FcRH5+/CD28+ MOLP-2 cells



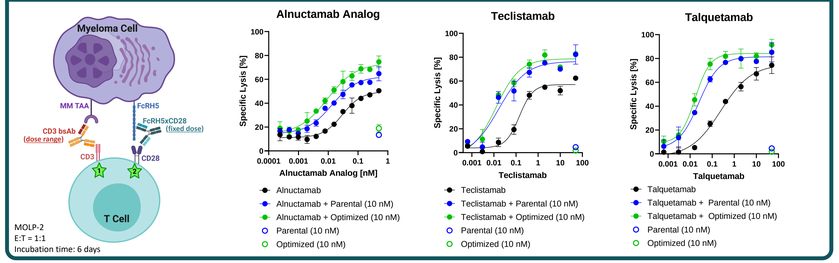
2. Balanced binding to human- and cyno-expressing PEAK cells, with no binding on PEAK expressing other FcRH family members



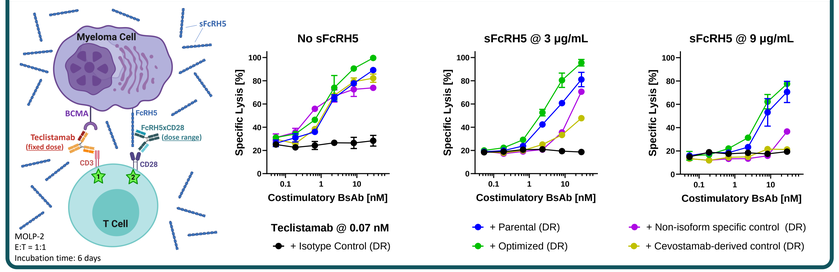
FcRH5xCD28 bsAbs bind FcRH5 independently of sFcRH5 competition



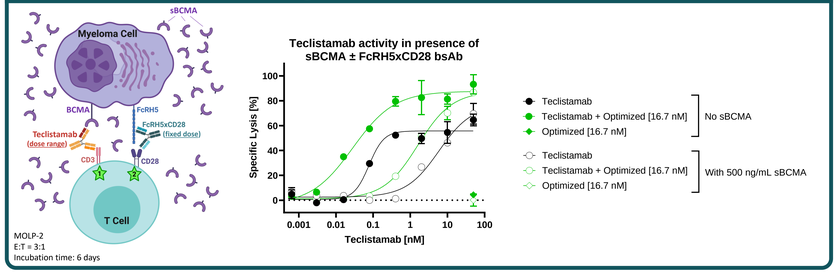
FcRH5xCD28 bsAbs enhance the activity of several TCEs



Synergy with Teclistamab observed in presence of sFcRH5



FcRH5xCD28 bsAb mitigates TCE activity loss induced by sBCMA



FcRH5xCD28 bsAbs bind FcRH5 independently of sFcRH5 competition

Status and next steps

- Identified anti-FcRH5 arms with high specificity to FcRH5 domain 9
- FcRH5-candidate arms paired with our anti-CD28 arm, showed robust synergy in killing FcRH5+ MM cells when combined with TCEs targeting BCMA or GPRC5D
- Demonstrated activity of FcRH5xCD28 bsAbs in the presence of soluble FcRH5
- Addition of FcRH5xCD28 bsAbs partially restored the activity of BCMA-targeting TCEs reduced by soluble BCMA, potentially overcoming a known resistance mechanism to TCEs in MM patients
- FcRH5xCD28 bsAb lead candidate has been selected, preclinical development and clonal cell line construction strategically set to begin in early 2025