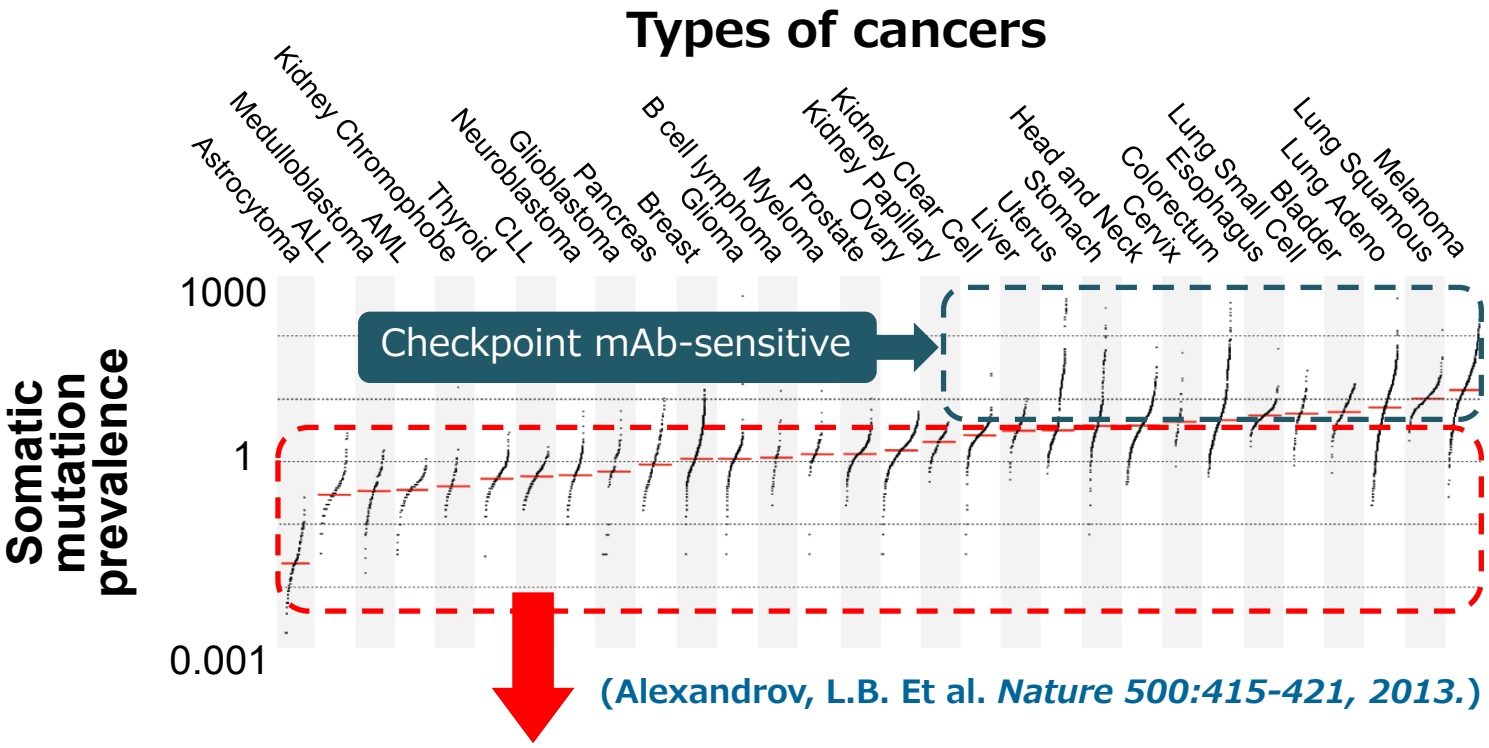
第26回抗悪性腫瘍薬開発フォーラム
2/16/2019, がん研究会がん研究所

CAR T cell therapy targeting the activated conformation of integrin beta 7 for multiple myeloma

Osaka University
Naoki Hosen

Beyond CD19 CAR T cells



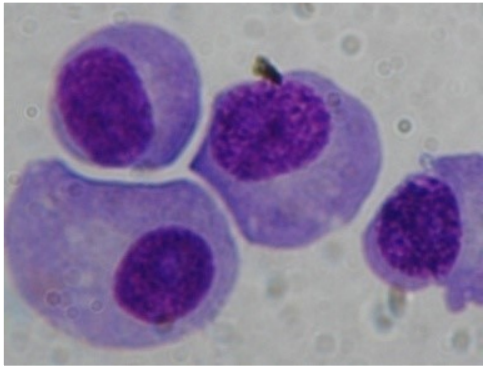
(Alexandrov, L.B. Et al. *Nature 500:415-421, 2013.*)

Good target for CAR T cell therapy

To identify an appropriate cancer-specific target antigen is the first and most critical step for developing CAR T cell therapy.

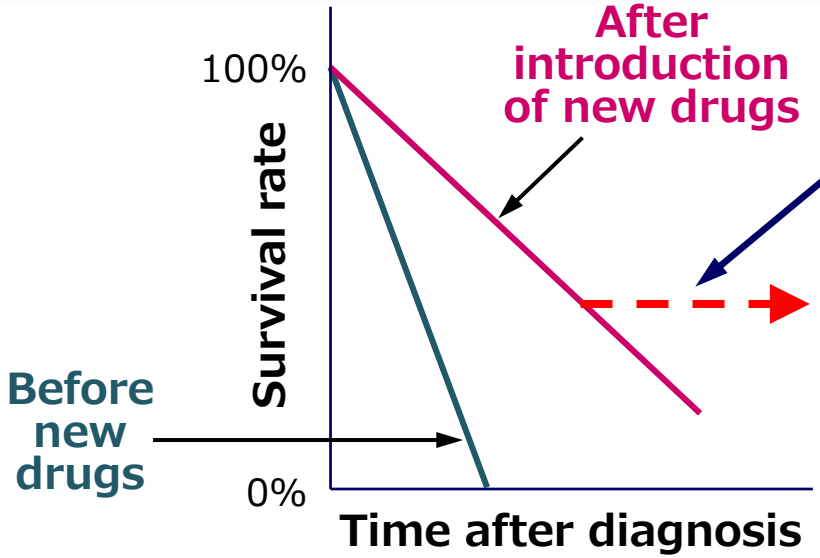
However, appropriate cancer-specific molecules were lacking in most cancers in spite of extensive search by transcriptome or proteome analysis.

Multiple Myeloma (MM)



Multiple myeloma(MM) : A hematological cancer derived from plasma cells（18,000 pts. in Jpn）

In spite of improvement of the prognosis by introduction of new drugs (proteasome inhibitors, immunomodulatory drugs), cure of MM is still difficult.



CAR T cell therapy is a promising strategy to cure MM.

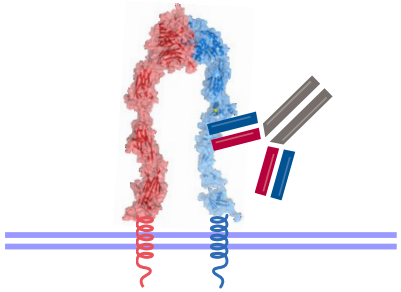
MM-specific cell surface antigens need to be identified to develop CAR T cell therapy

Identification of a multiple myeloma-specific antigen

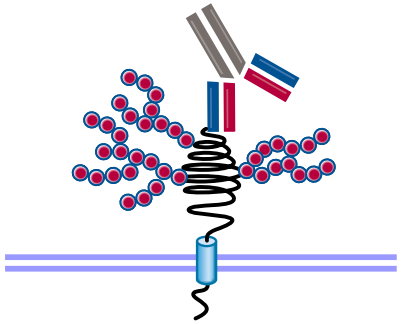
No MM-specific molecules remain unidentified after extensive search by transcriptome or proteome analysis

MM-specific antigens formed by post-translational events may have been missed

Myeloma cells mRNA **vs.** Normal cells mRNA



Conformational change



Glycosylation

Identify MM-specific mAbs first, then clarify the character of the antigens recognized by them

Identification of MMG49 as a novel MM-specific mAb

Establishment of mAbs that react with MM cell lines (>10,000 clones)

↓

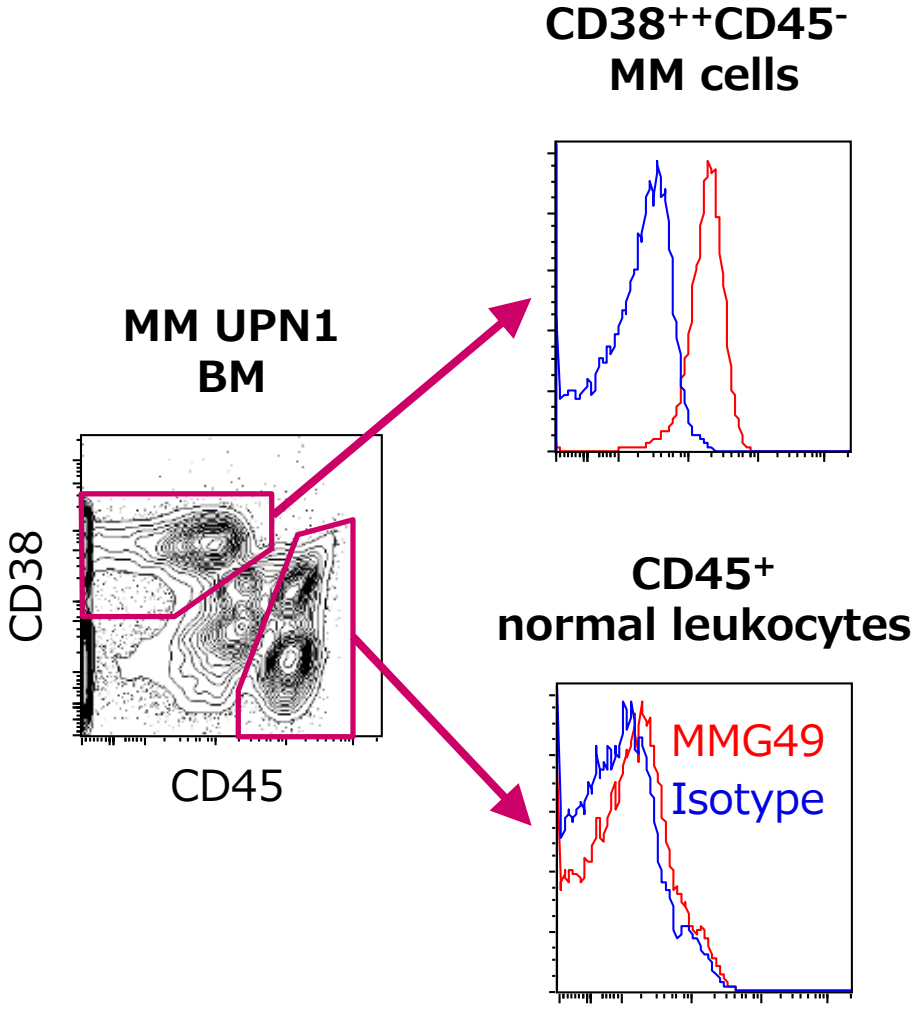
1st screening: mAbs that do not react with PBMCs from healthy donors (~500 clones)

↓

2nd screening: mAbs that react with MM cells but not with CD45+ normal leukocytes in BM of MM patients

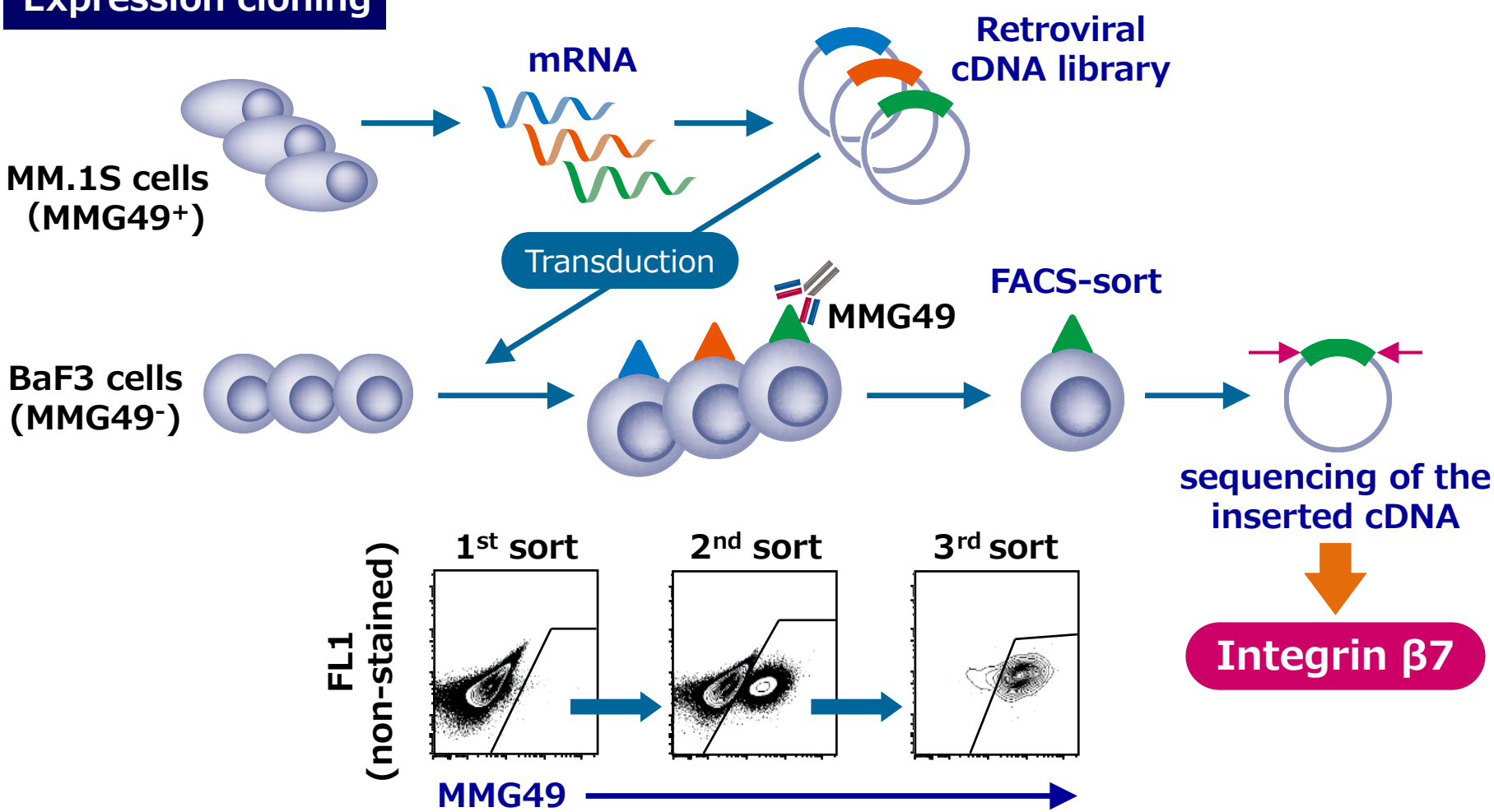
↓

MMG49



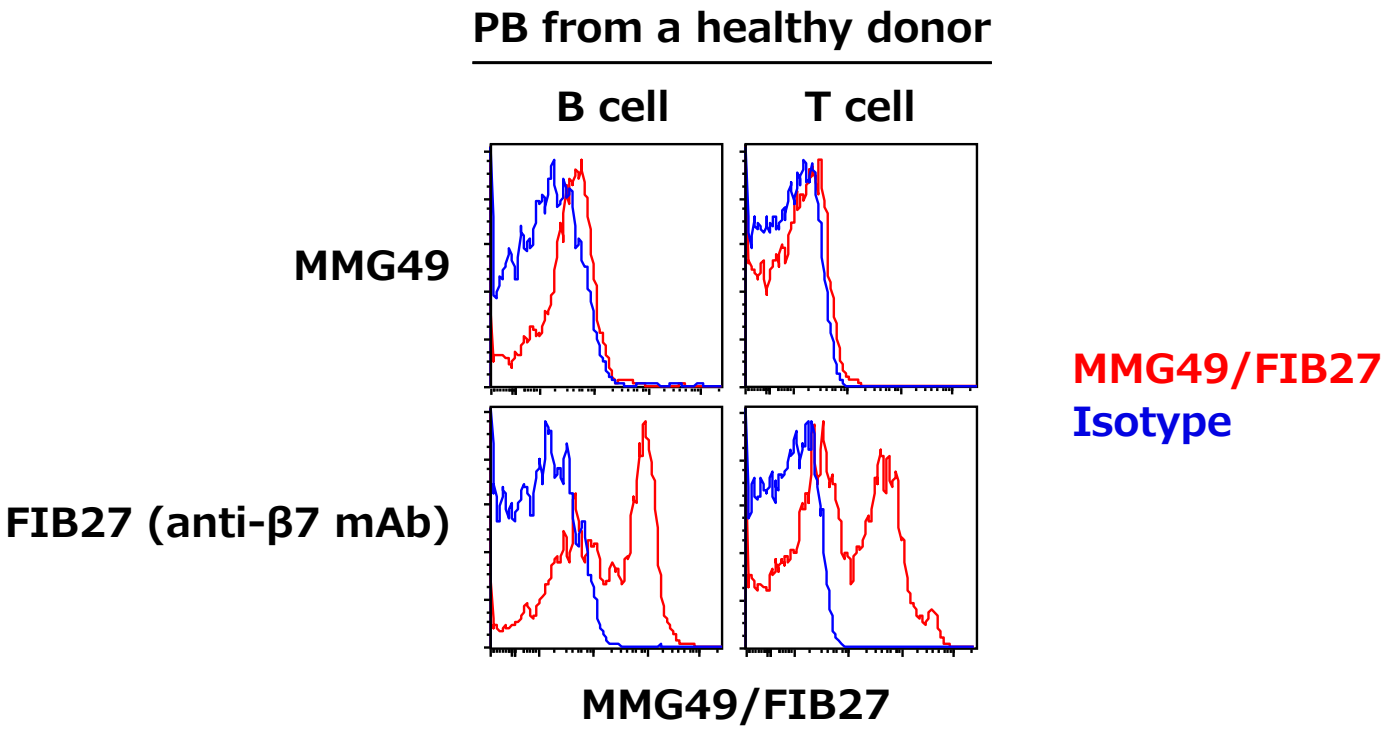
MMG49 recognizes integrin β7

Expression cloning



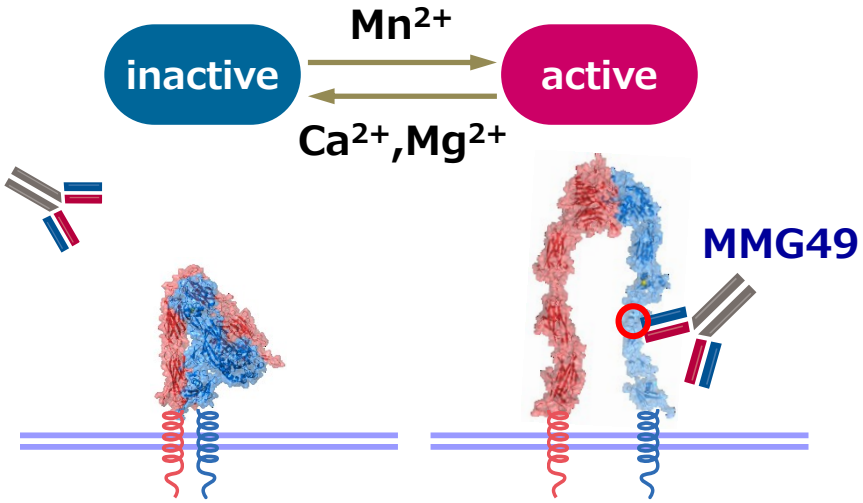
? Integrin β7 is reportedly expressed in subsets of normal lymphocytes.

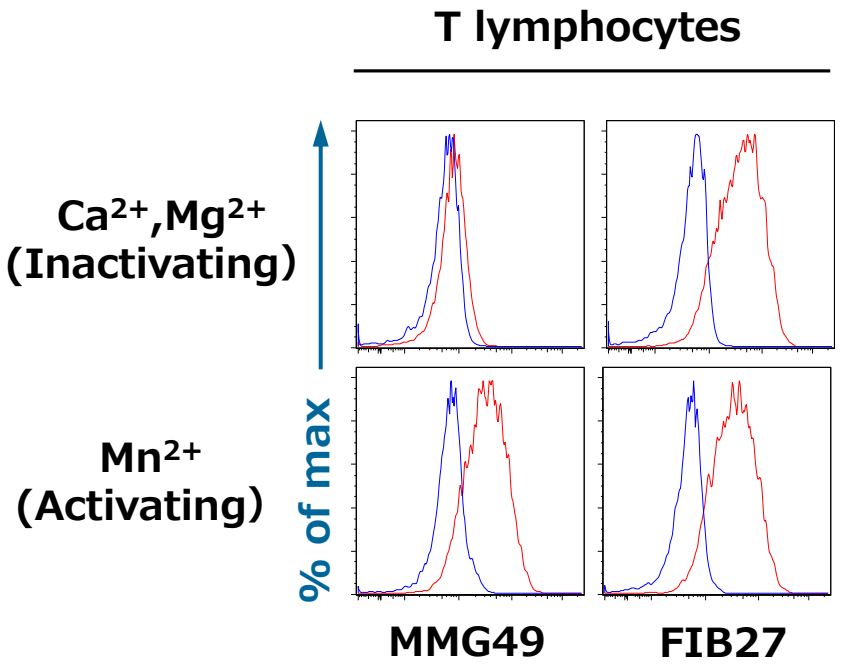
MMG49 recognizes integrin β7, but does not react with normal lymphocytes expressing integrin β7



	T cell	B cell	Eo	NK cell	CD34⁺ HPCs	MM
MMG49	−	−	−	−	−	++
FIB27 (anti-β7)	+	+	+	+	+	++

MMG49 is specific for the activated conformation of integrin β7





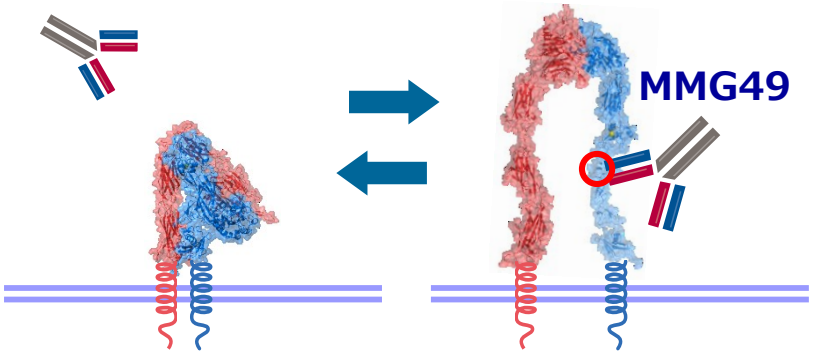
Collaboration with Prof. Junichi Takagi, Institute for Protein Research, Osaka Univ.

Integrin β7 is constitutively activated in MM

Normal lymphocytes

Inactivating condition (Ca^{2+},Mg^{2+})

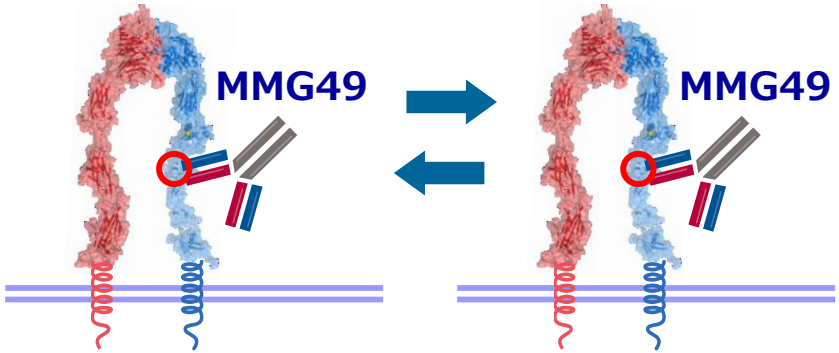
Activating condition (Mn^{2+})



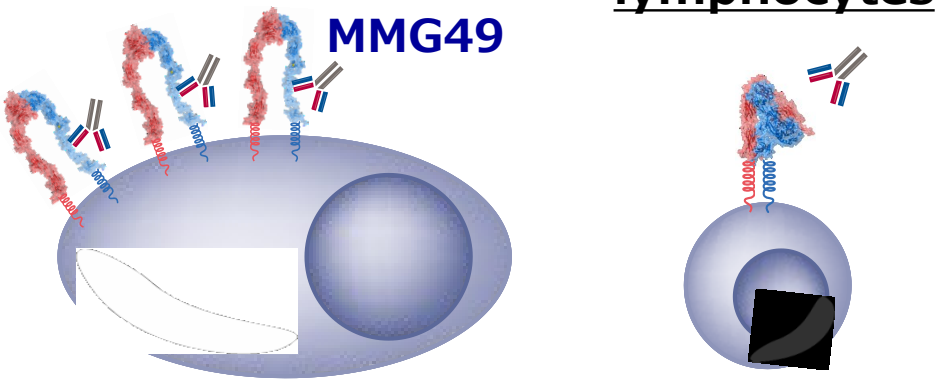
MM cells

Inactivating condition (Ca^{2+},Mg^{2+})

Activating condition (Mn^{2+})

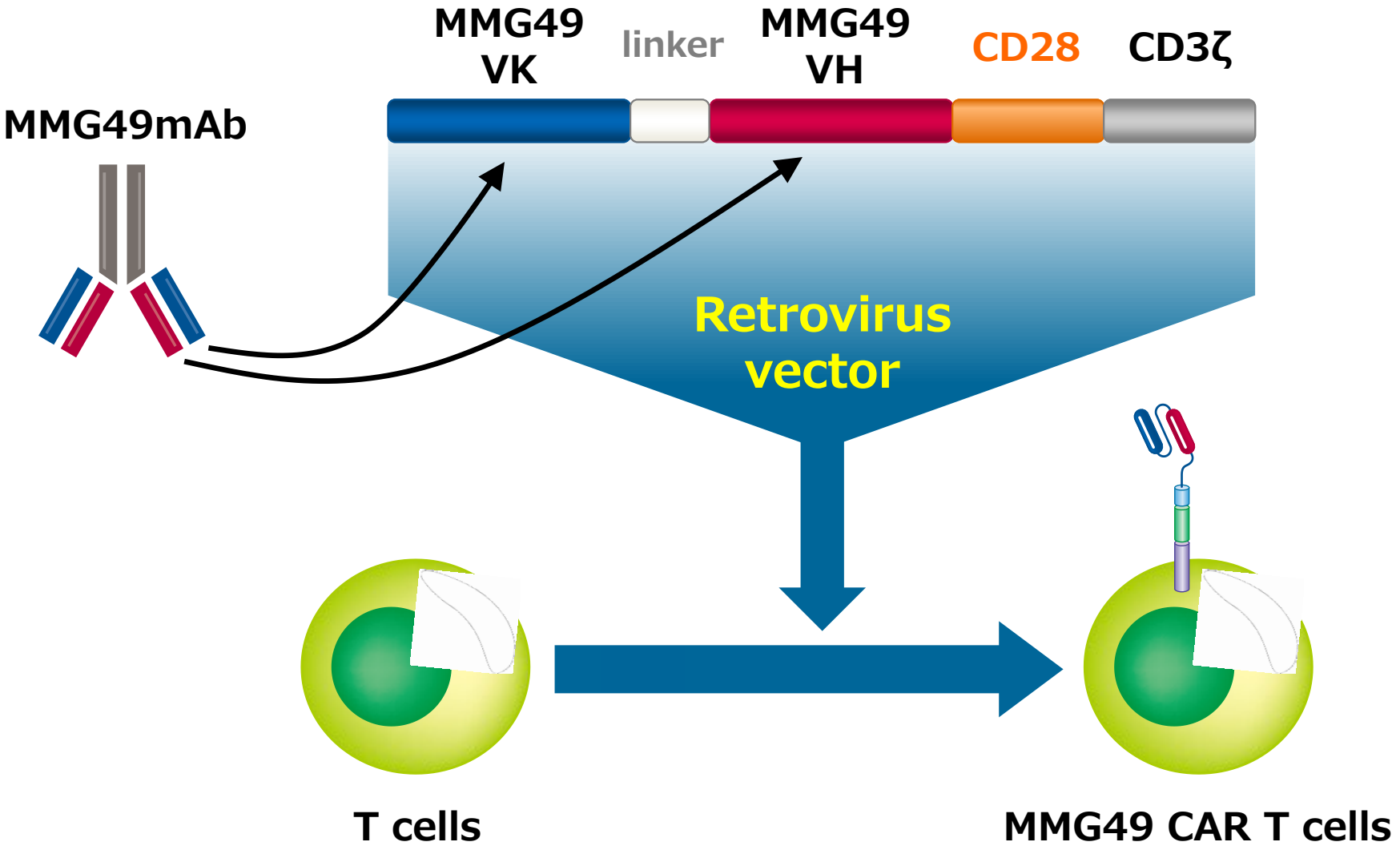


Elevated expression levels and constitutive activation of integrin β7 are responsible for high specificity of MMG49 to MM cells

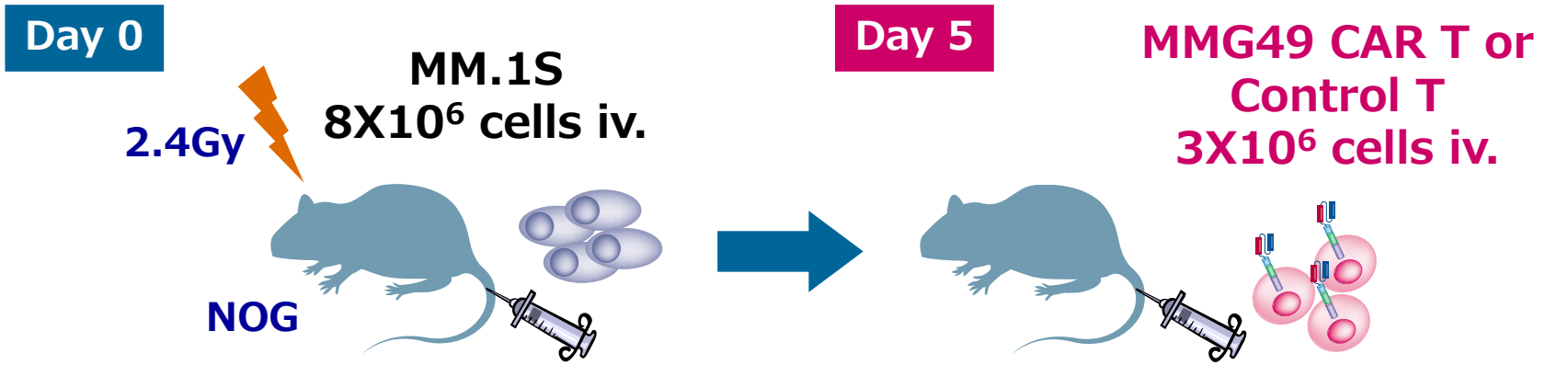


	MM	Normal lymphocytes
Integrin β7 expression	high	low
Integrin β7 Activation state	active	inactive
MMG49-binding	++	-/lo

MMG49 CAR T cells

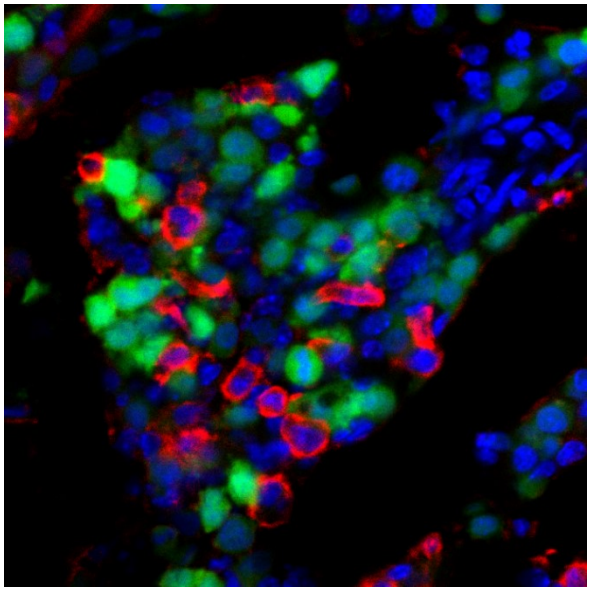


In vivo anti-MM effect of MMG49 CAR-T cells

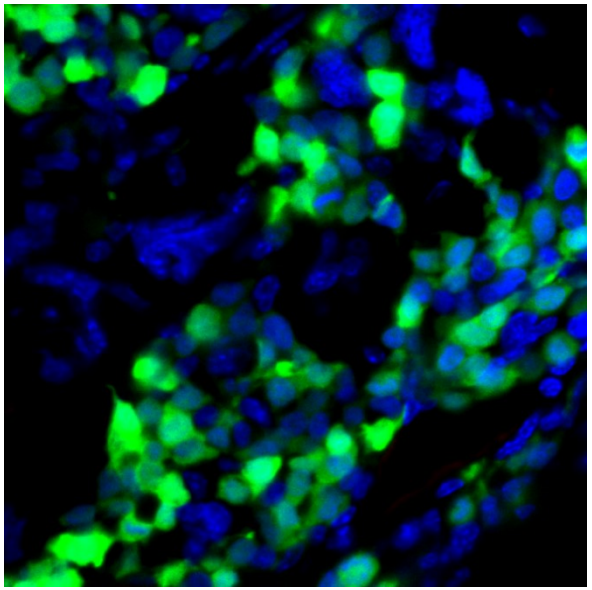


BM 5 days after CAR T cell injection

MMG49CAR T



Control T



CAR T cells

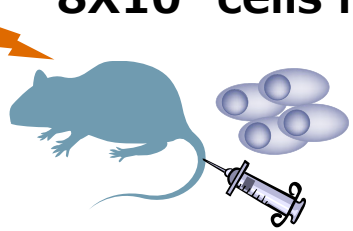
MM cells

In vivo anti-MM effect of MMG49 CAR T cells

Day 0

MM.1S-luc-GFP
8X10^6 cells iv.

2.4Gy

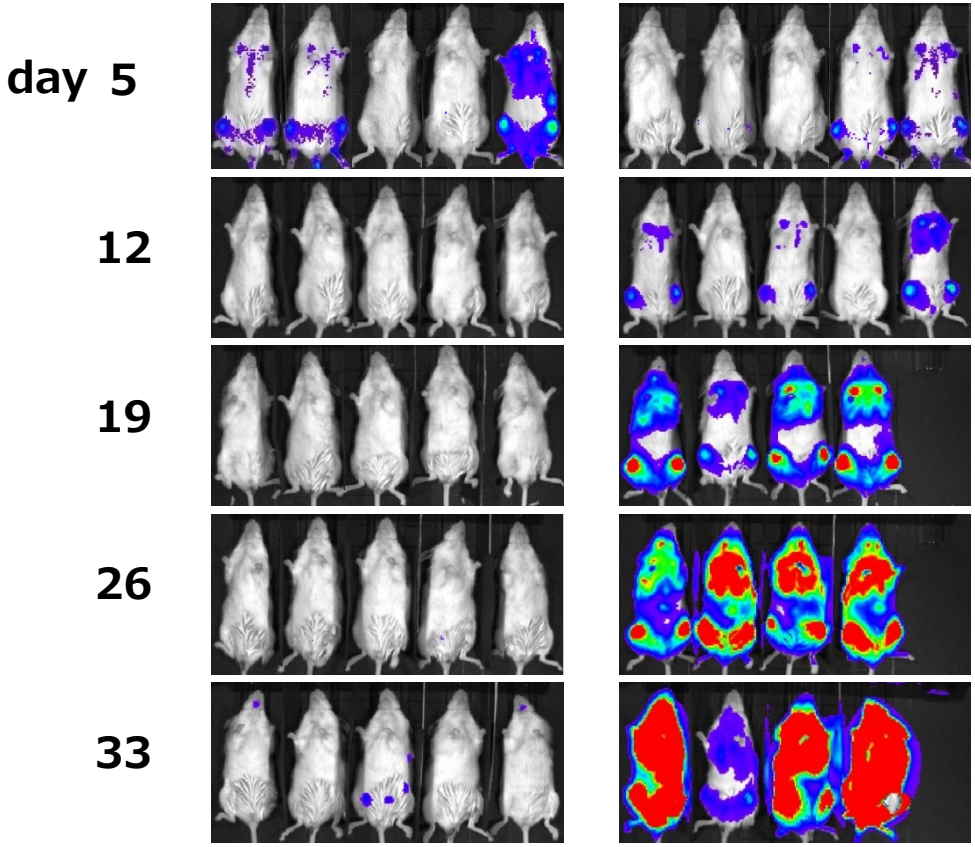


Day 5

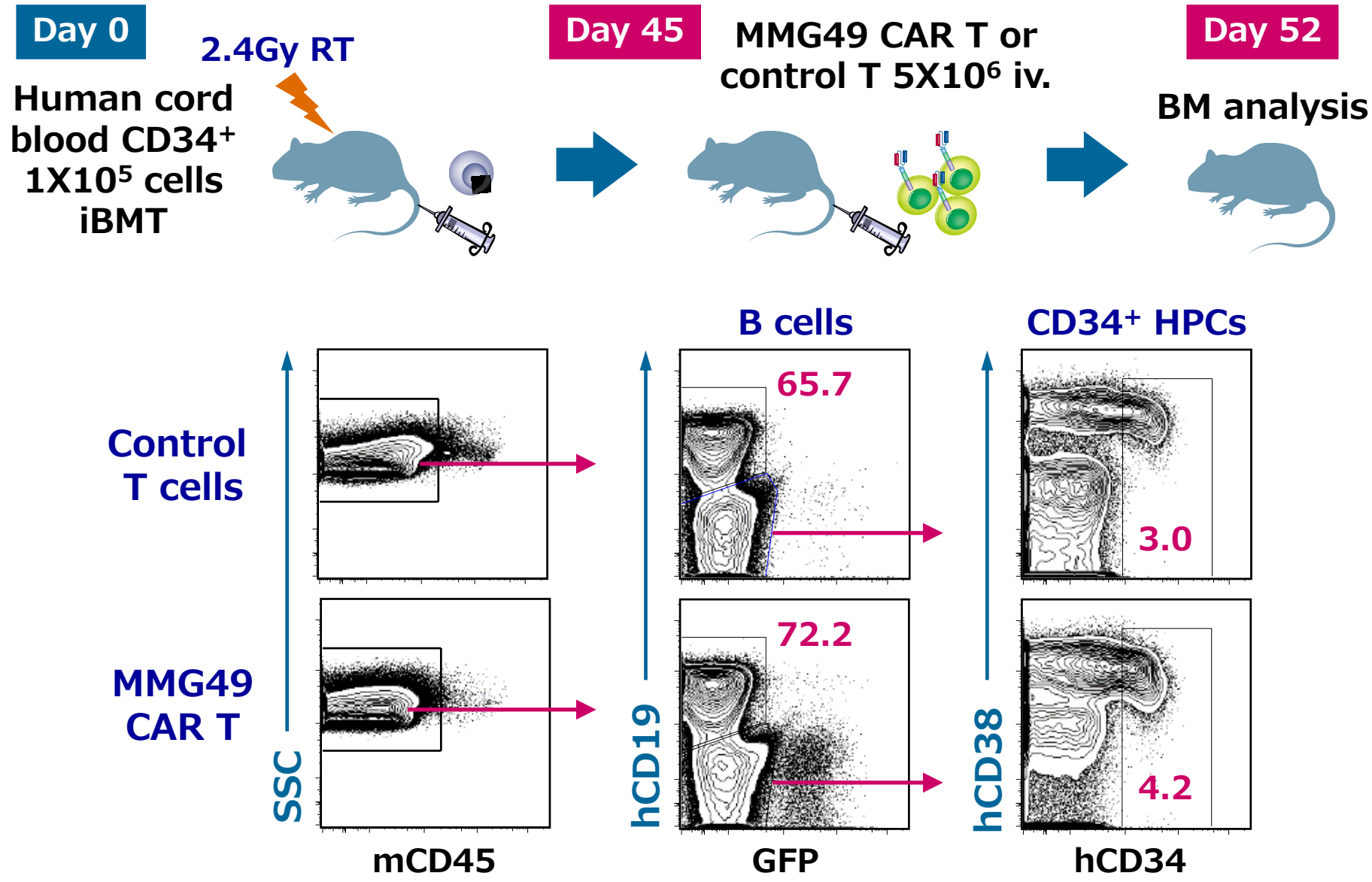
MMG49 CAR T or
control T 3X10^6 iv.

Every week

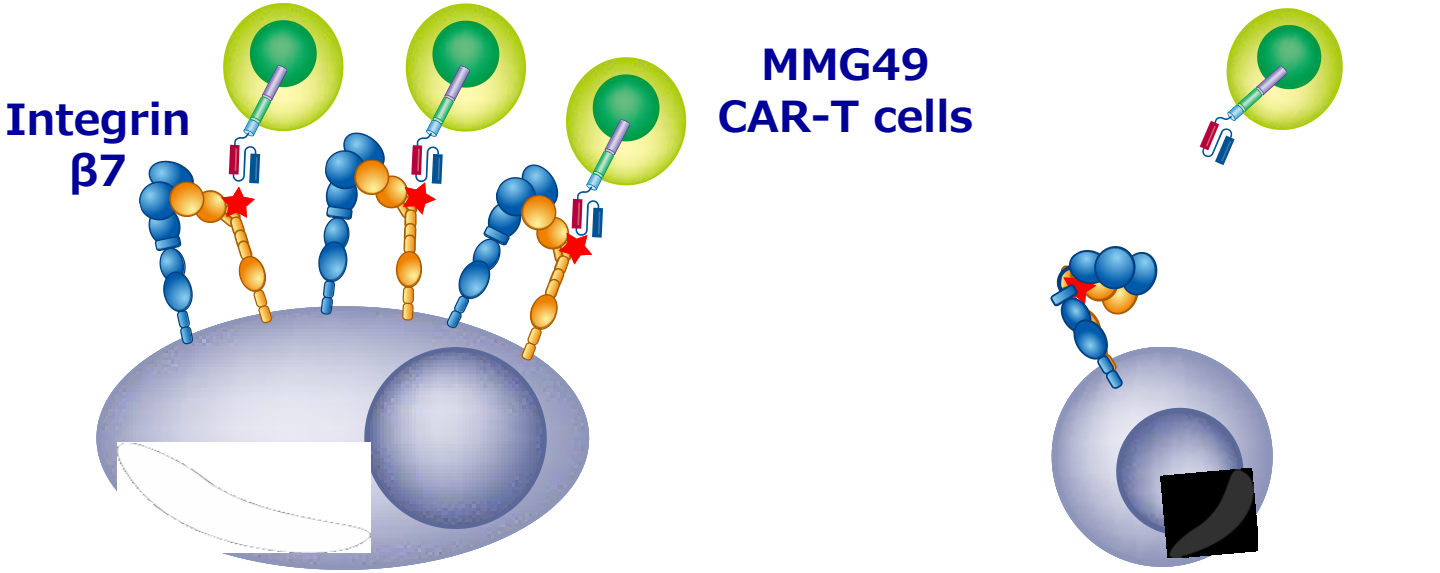
IVIS



MMG49 CAR-T cells do not damage normal hematopoietic cells



CAR T-cell therapy targeting the active conformation of integrin β7 is promising for MM.



H28-30 pre-clinical tests in an AMED-funded project

H30/8 transfer to a pharmaceutical company

Cancer immunotherapeutic targets may yet be identified in many cell surface proteins that undergo conformational changes, even if the expression of the proteins themselves is not cancer-specific.

Hosen, N., et al. *Nature medicine 23: 1436-1443, 2017*