Terapia mediata da anticorpi nel Mieloma Multiplo: Indicazioni dalla ricerca di base

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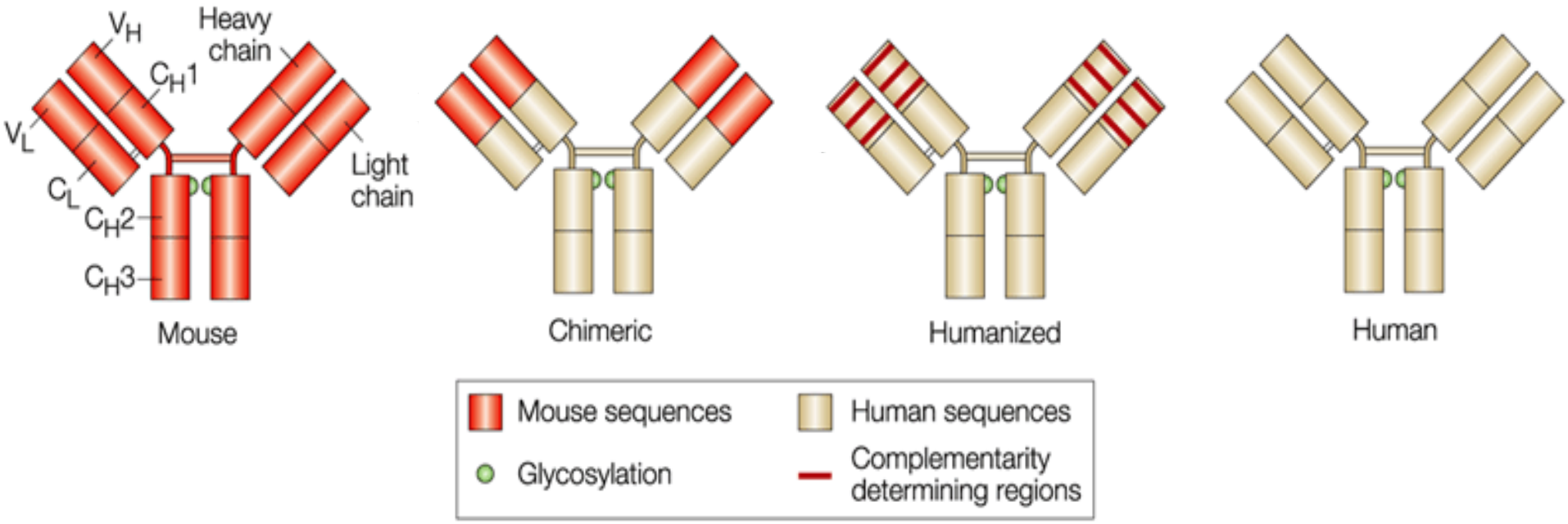
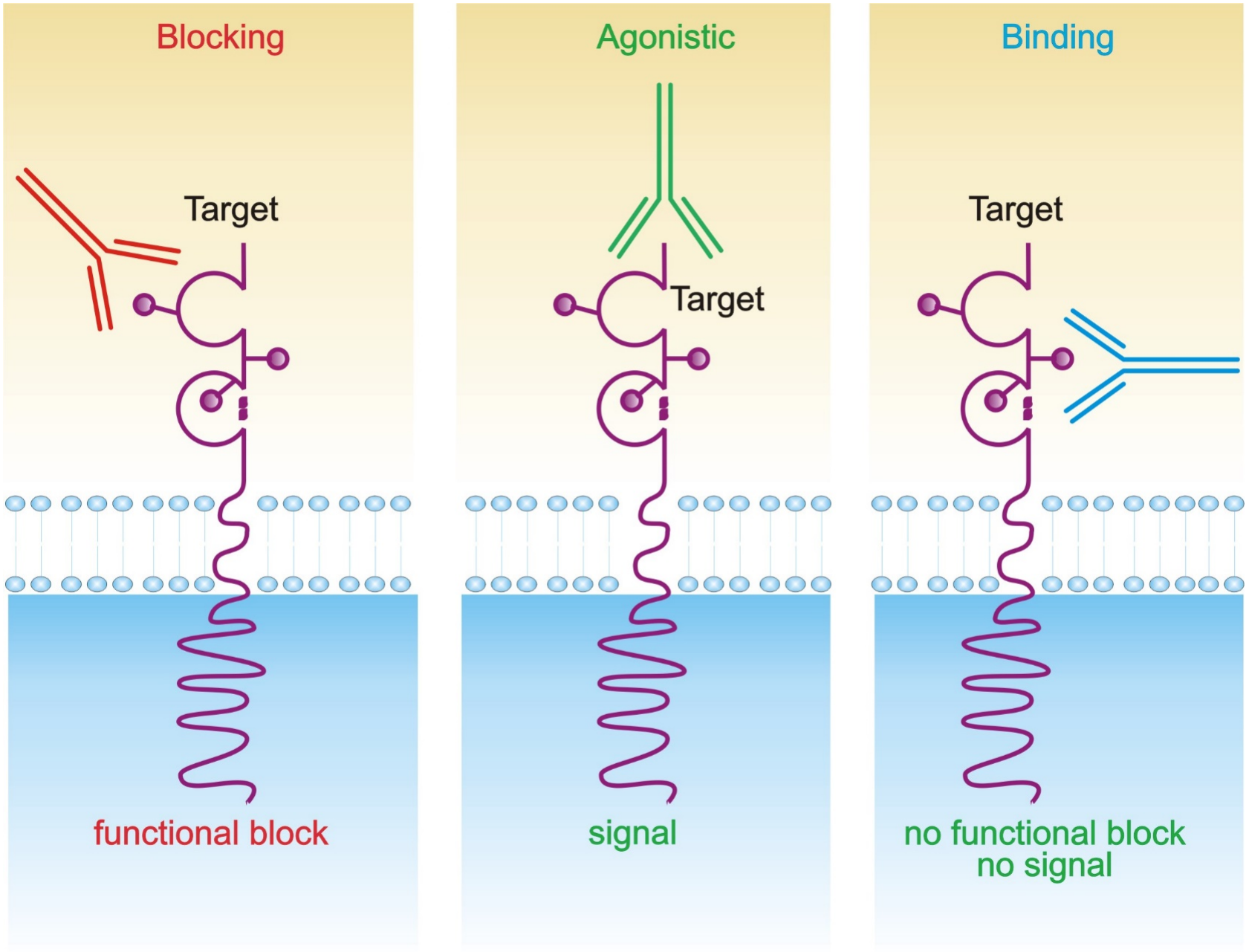
Therapeutic monoclonal antibodies: reducing immunogenicity



decreasing immunogenicity

Imai & Takaoka. Nature Reviews Cancer 2006; 6: 714-727

Events occurring after target binding by monoclonal antibodies



Immunomodulatory properties of antibodies

1) Tumors shield themselves from the immune system through immunosuppressive mechanisms in the tumor microenvironment, for example, shedding of surface molecules

2) Antibodies that target not only the tumor, but immunoregulatory pathways mediated by cells of the immune system, provided therapeutic successes

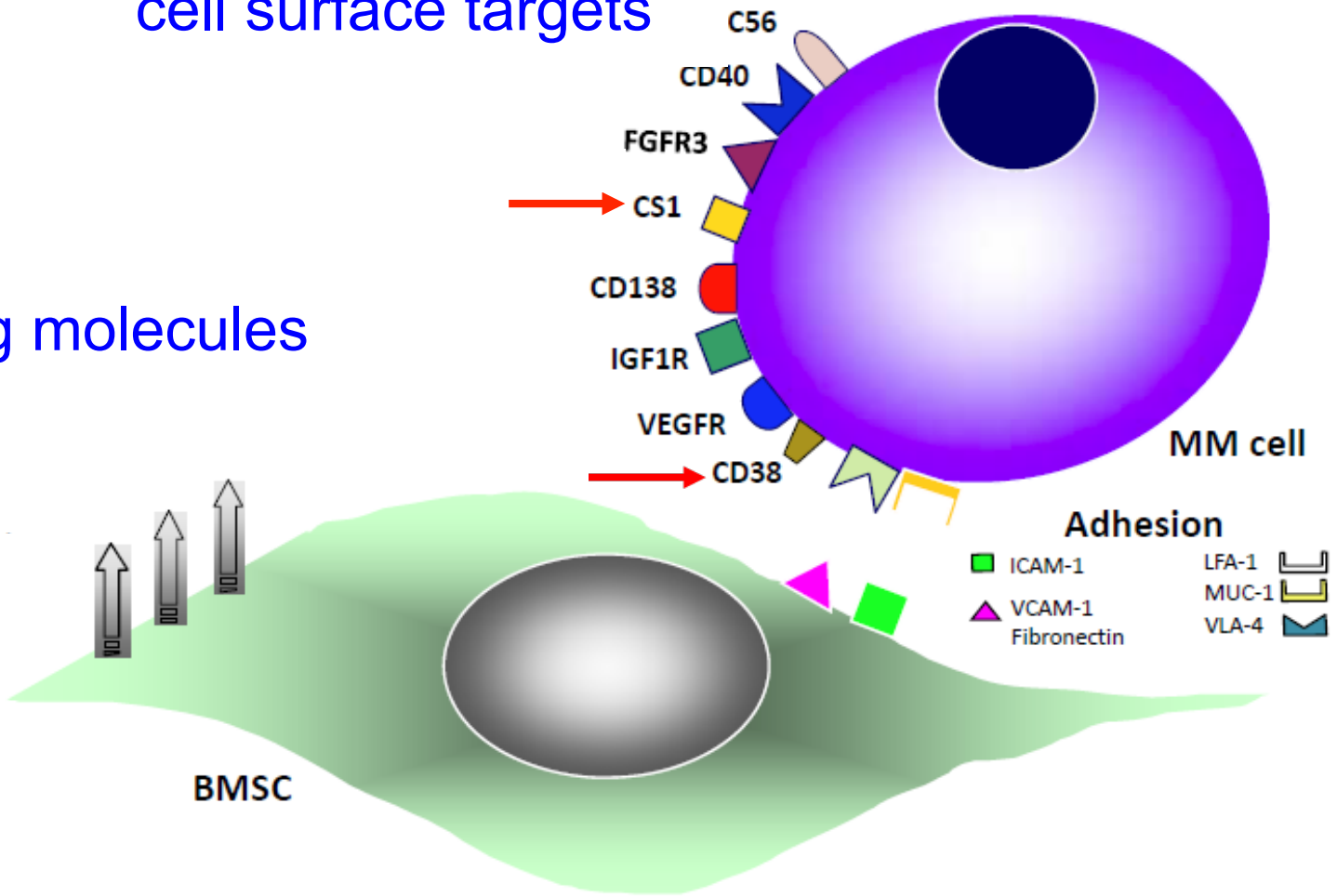
3) CD38 is both a target molecule in myeloma and at the same time an immunomodulatory receptor in immunity

Targets for monoclonal antibody therapy in myeloma

cell surface targets

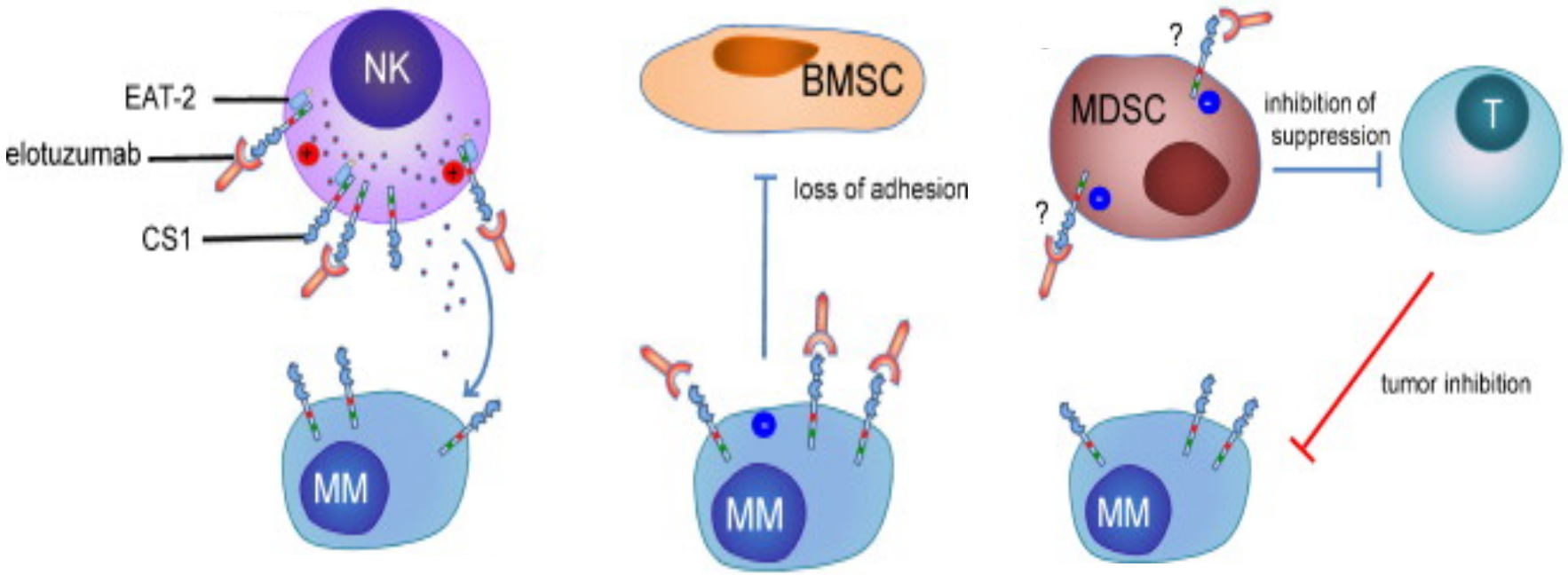
signaling molecules

IL-6
RANKL
DKK1
VEGF
IGF-1
SDF-1α
BAFF, APRIL



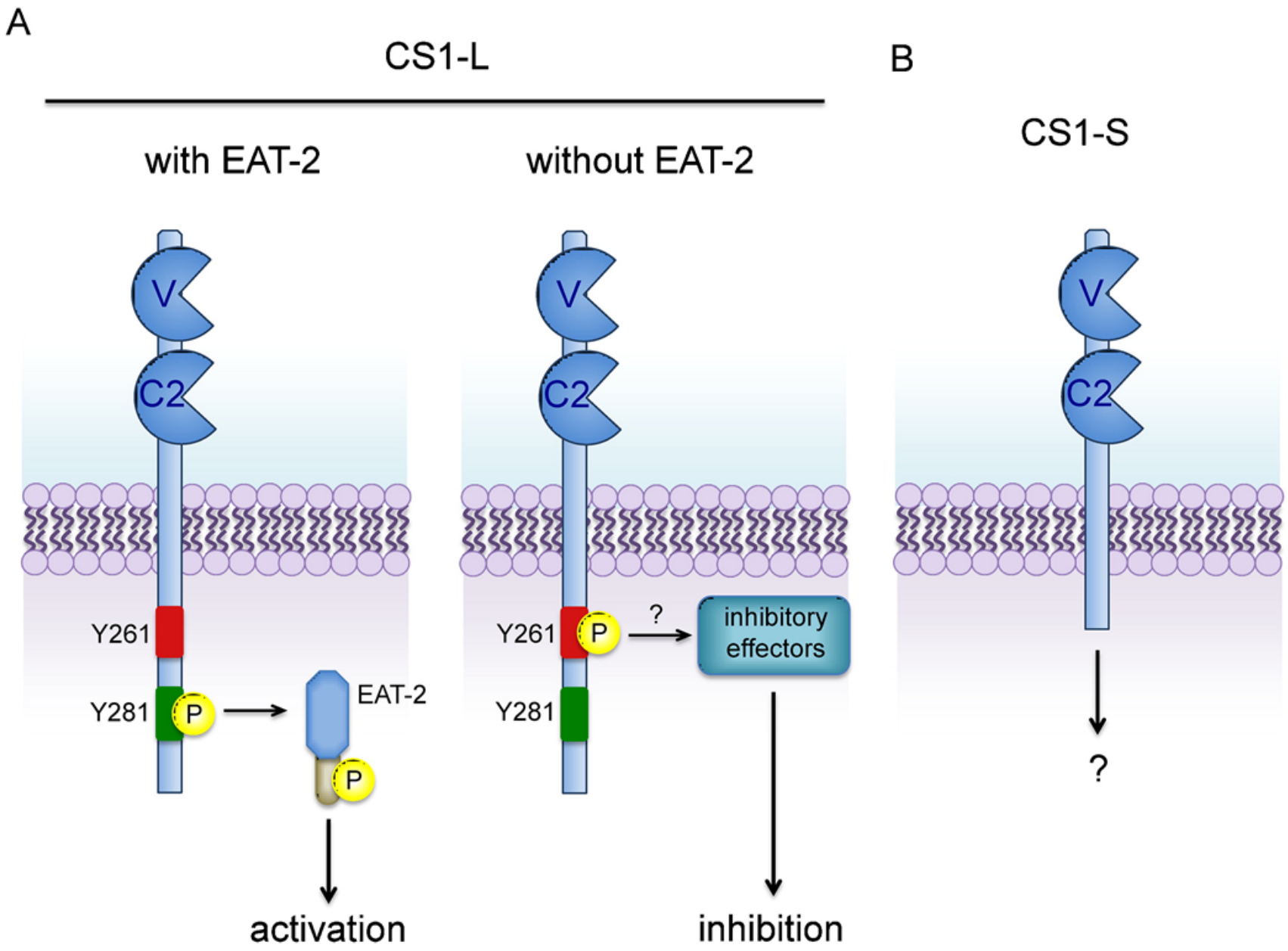
Adapted from: Anderson KC. J Clin Oncol 2012;30:445-452

Mechanisms of action by elotuzumab (anti-CS1/SLAMF7) mAb in multiple myeloma



Guo et al. Mol Cell Biol. 2015 Jan;35(1):41-51

Two CS1 (SLAMF7) isoforms differentially regulate immune cell functions



Guo et al. Mol Cell Biol. 2015 Jan;35(1):41-51

Rationale for targeting CD38

Functions:

1) Receptor-mediated adhesion and signaling functions

2) Enzymatic activities

   Contributes to intracellular calcium mobilization

   Involved in production of adenosine: important for induction of local immunological tolerance → implicated in local survival strategy of the neoplastic plasma cell in the bone marrow milieu

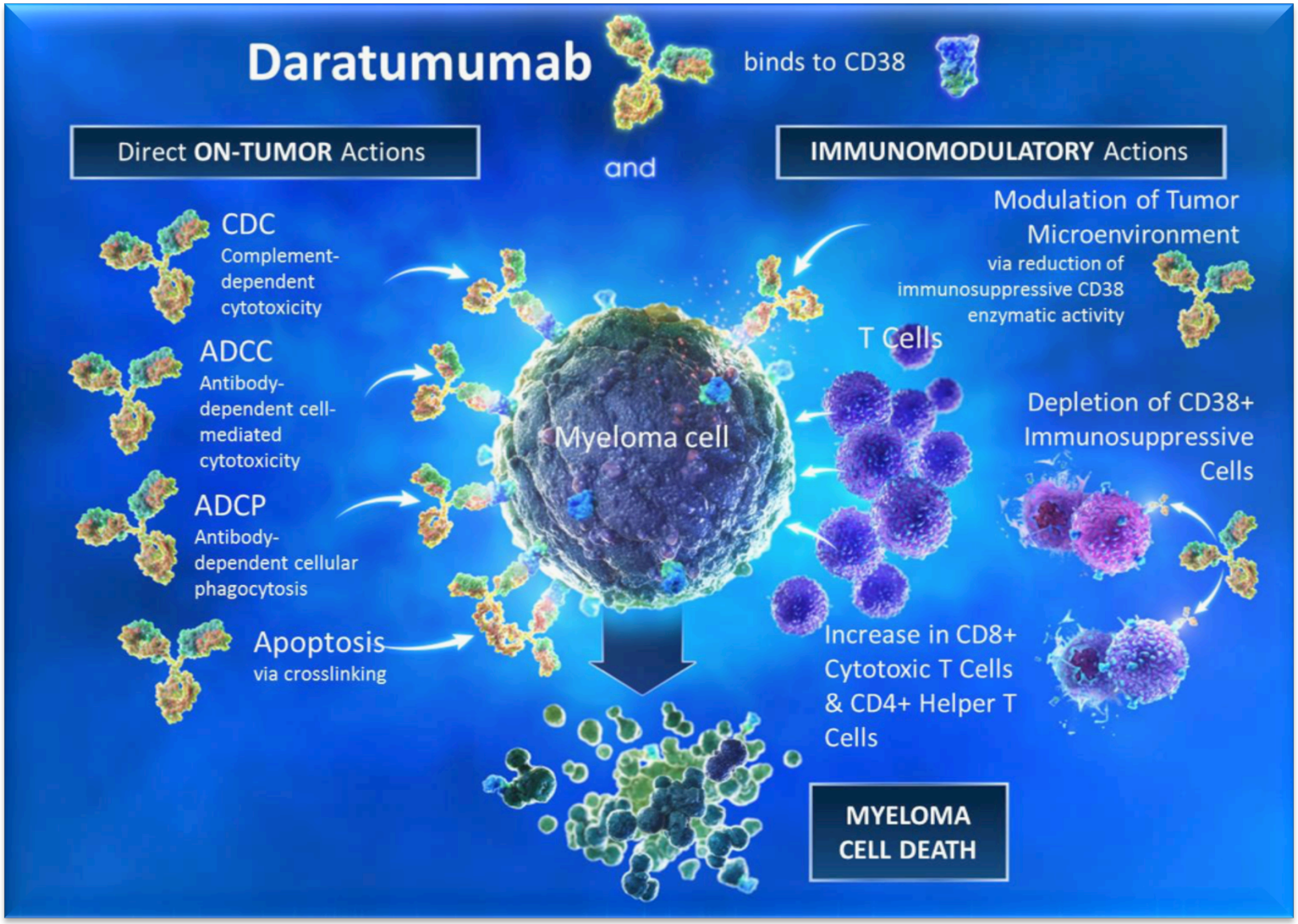
Expression levels:

1) Low expression of CD38 on lymphoid and myeloid cells under normal conditions

2) High expression of CD38 on multiple myeloma cells

References: Malavasi et al., Physiol Rev 2008; de Weers et al. J Immunol 2011;186: 1840-1848; Chillemi et al Mol Med 2013;19:99-108; Quarona et al Ann N Y Acad Sci 2015;1335:10-22, Van De Donk et al., Blòood, 2015; Horenstein et. al., Mol Med, 2016

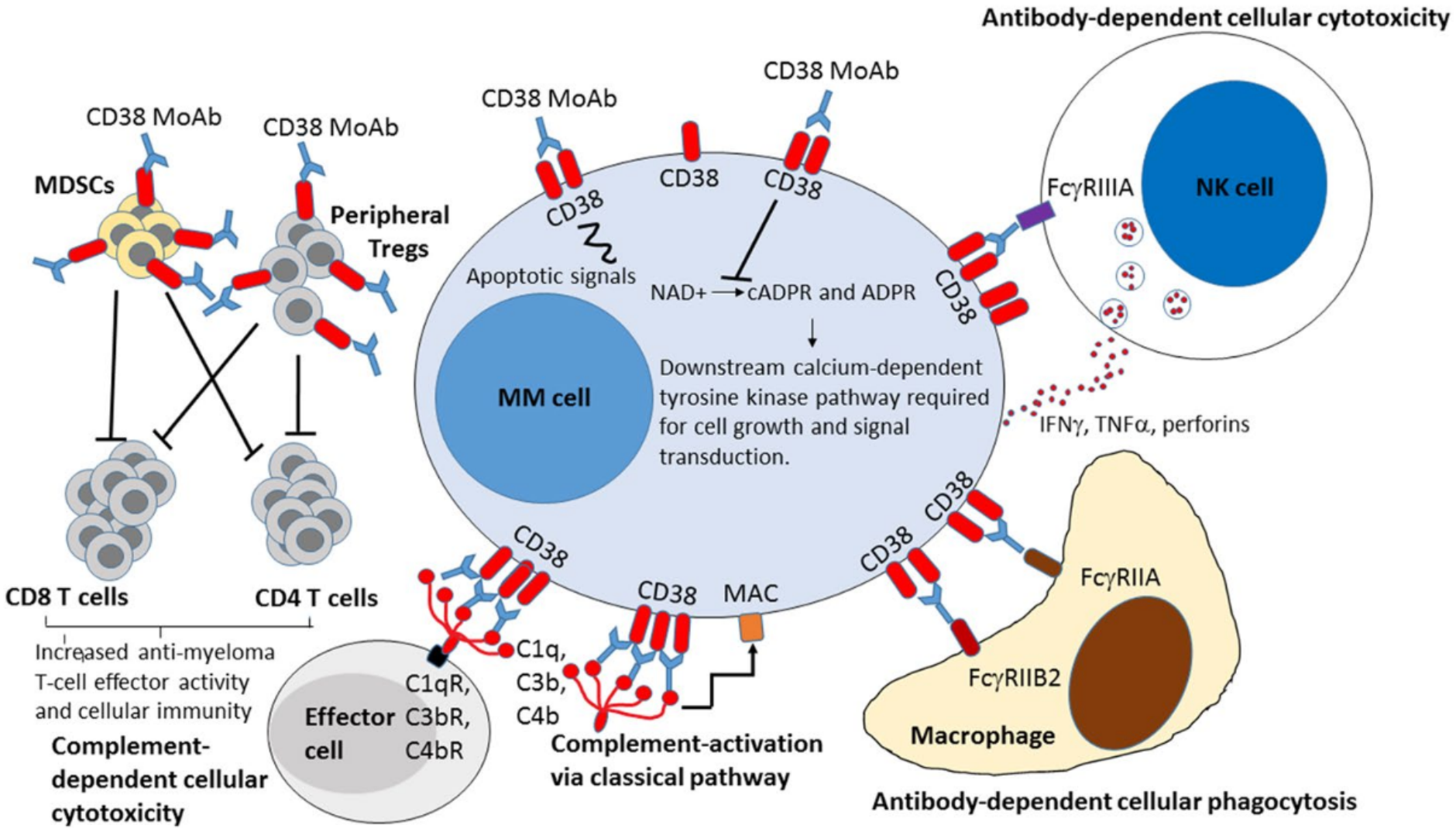
Mechanisms of action



Human CD38 is an IgGκ monoclonal antibody Direct and indirect antimyeloma activity
Depletes CD38^{+} immunosuppressive regulatory cells Promotes T-cell expansion and activation

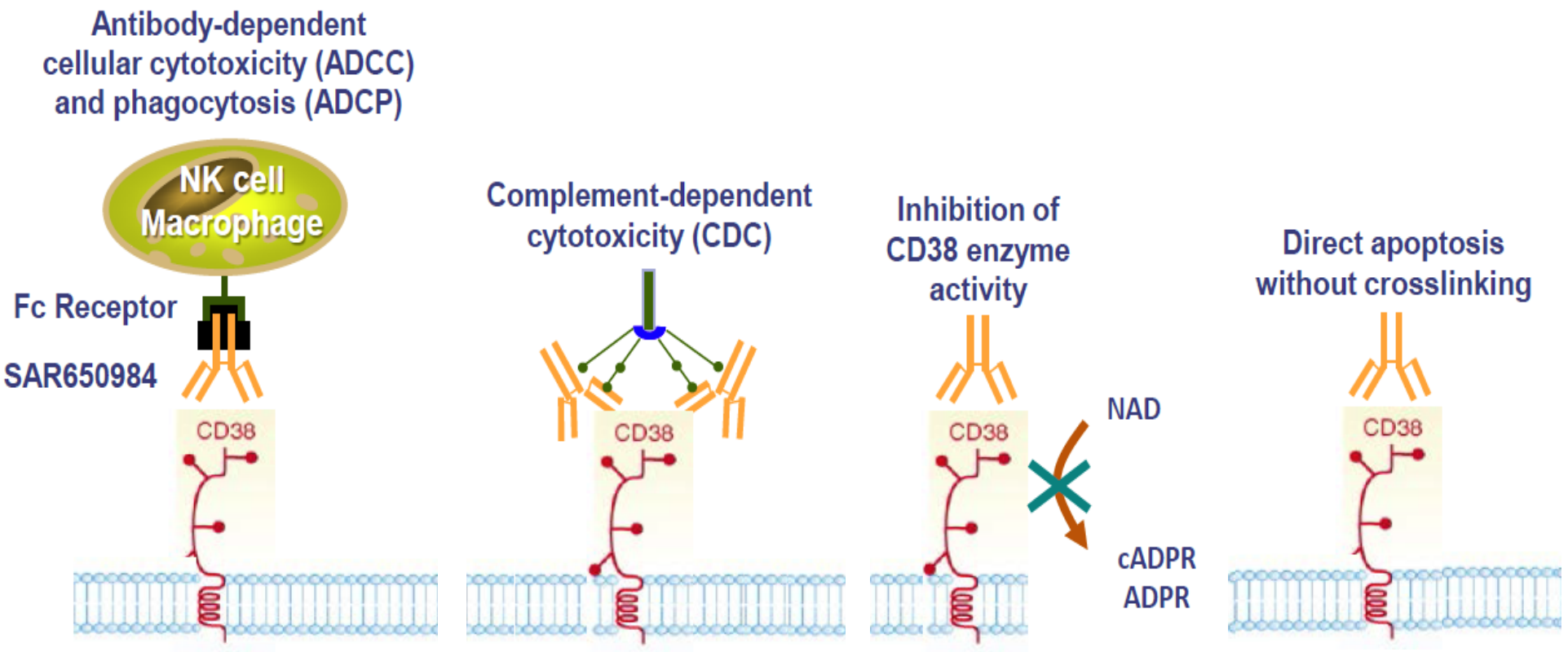
Lammerts van Bueren J, et al. *Blood*. 2014;124:Abstract 3474; Jansen JMH, et al. *Blood*. 2012;120:Abstract 2974; de Weers M, et al. *J Immunol*. 2011;186:1840-1848; Overdijk MB, et al. *MAbs*. 2015;7:311-321; Krejcik J, et al. *Blood*. 2016. Epub ahead of print.

Multi-faceted properties of CD38 MoAbs.



Shallis RM, Terry CM, Lim AH,Cancer Immunol Immunother. 2017

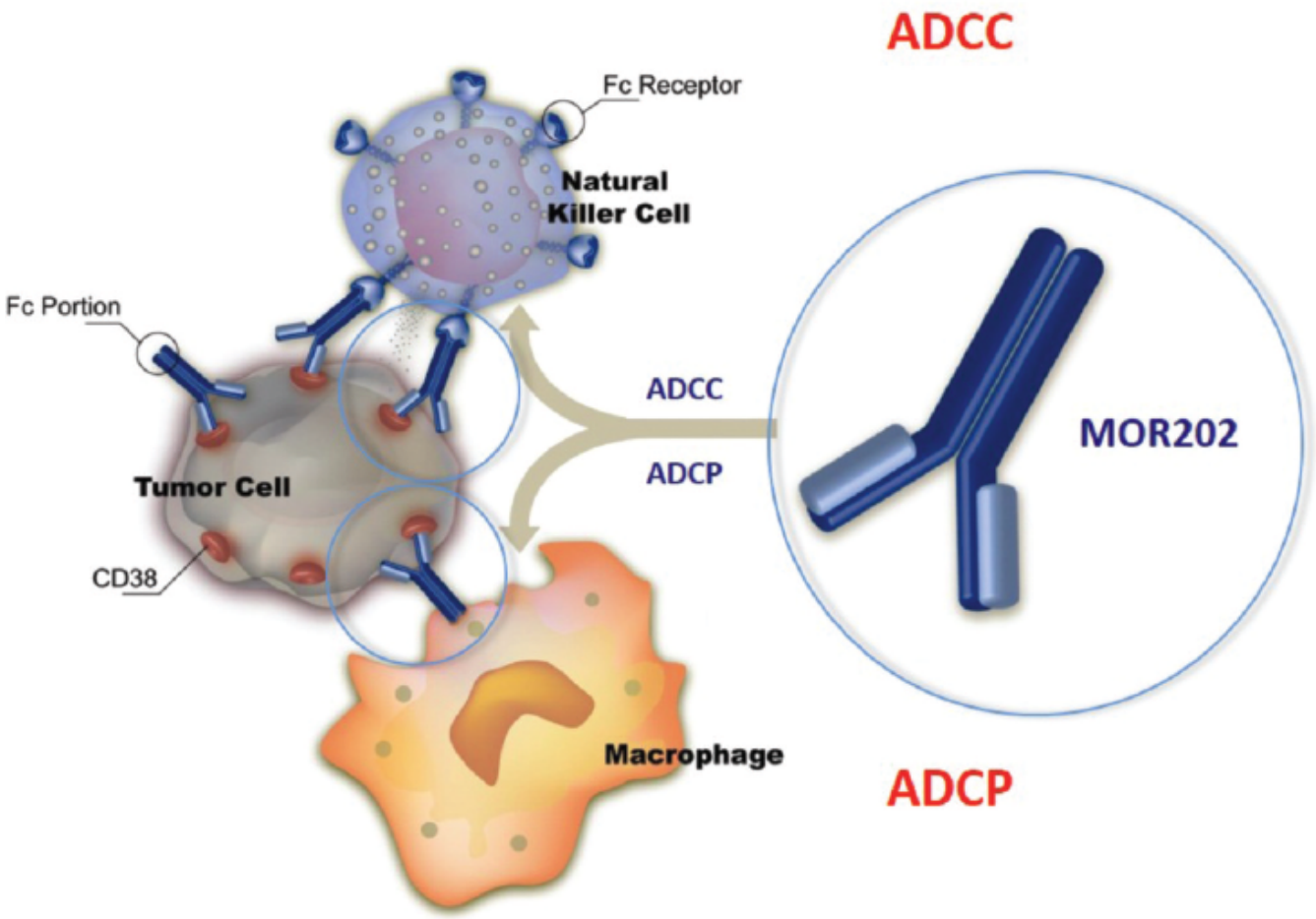
Isatuximab (anti-CD38) induces direct apoptosis and suppresses Tregs to mitigate immune impairment in multiple myeloma



Canonical and lysosome-dependent cell death*

Deckert et al. Clin Cancer Res 2014;20(17):4574-83; Martin et al. ASH 2014 oral presentation; Jiang et al. Leukemia 2015
X. Feng and K.C. Anderson, Clin Cancer Res, 2017

MOR202 (anti-CD38) mAb: main modes of action



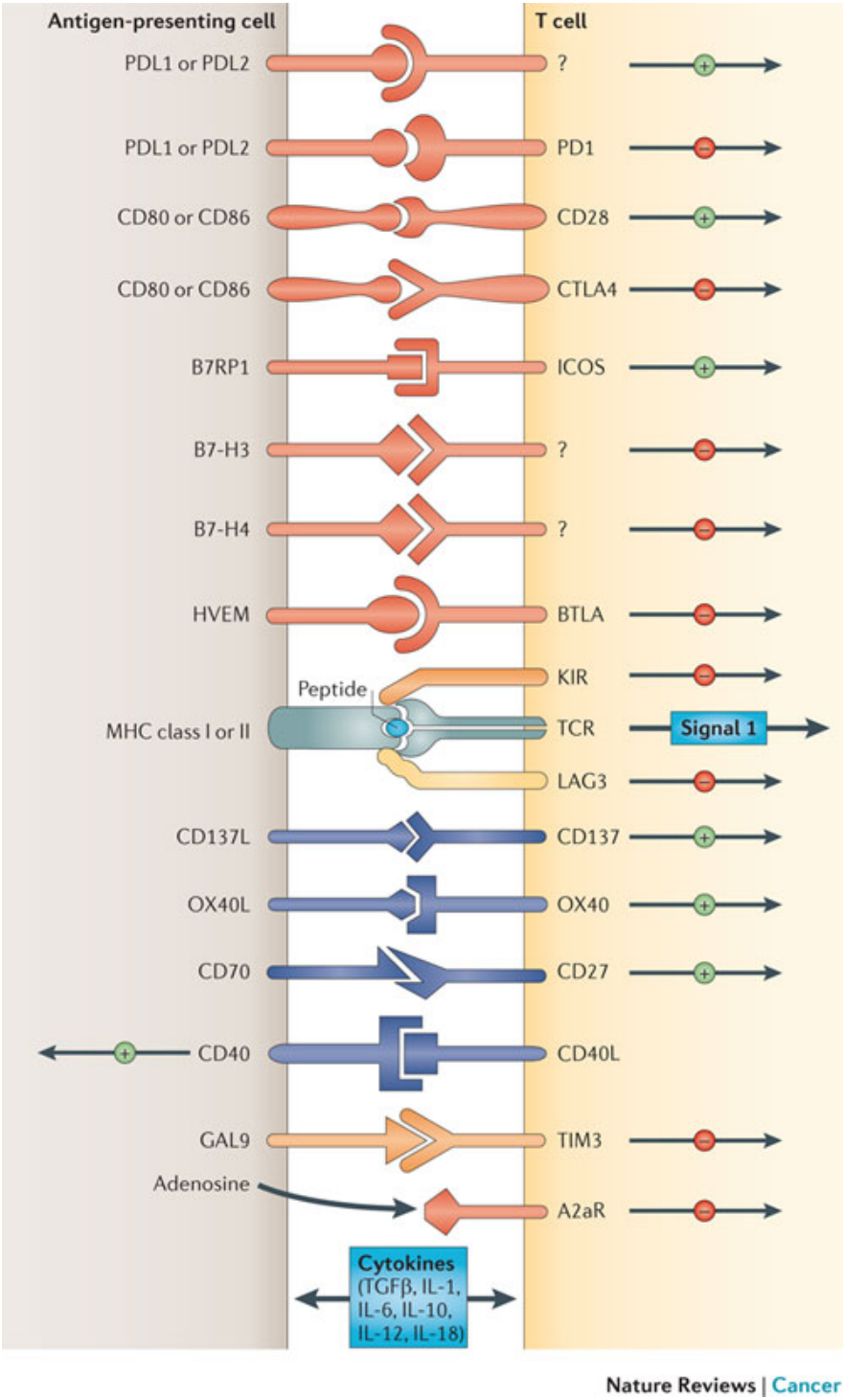
antibody-dependent cellular cytotoxicity (ADCC)

phagocytosis (ADCP)

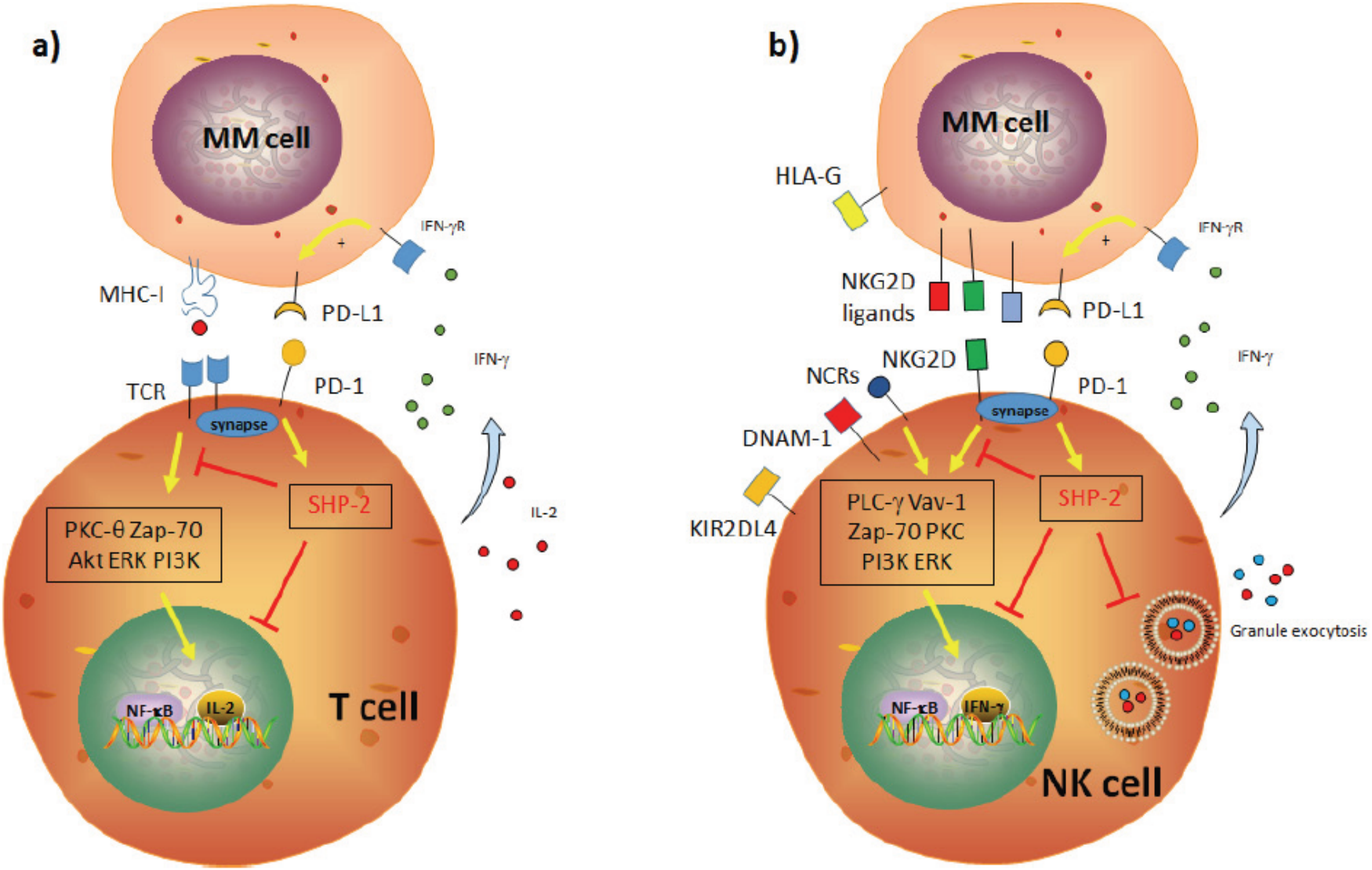
Raab et al. ASCO 2015 (Abstract 8574), poster presentation

Multiple co-stimulatory and inhibitory interactions regulate T cell responses

Purdell D., Nat Rev Cancer, 2012

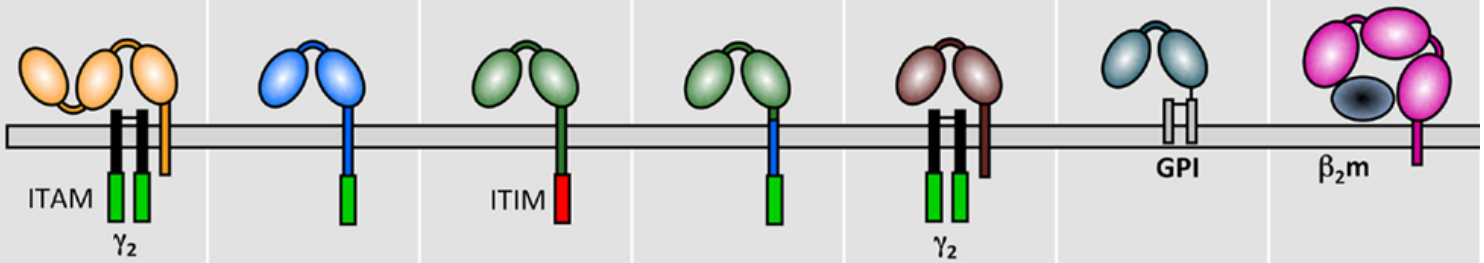


Impact of the PD-1/PD-L1 axis on T and NK cell cytotoxic functions



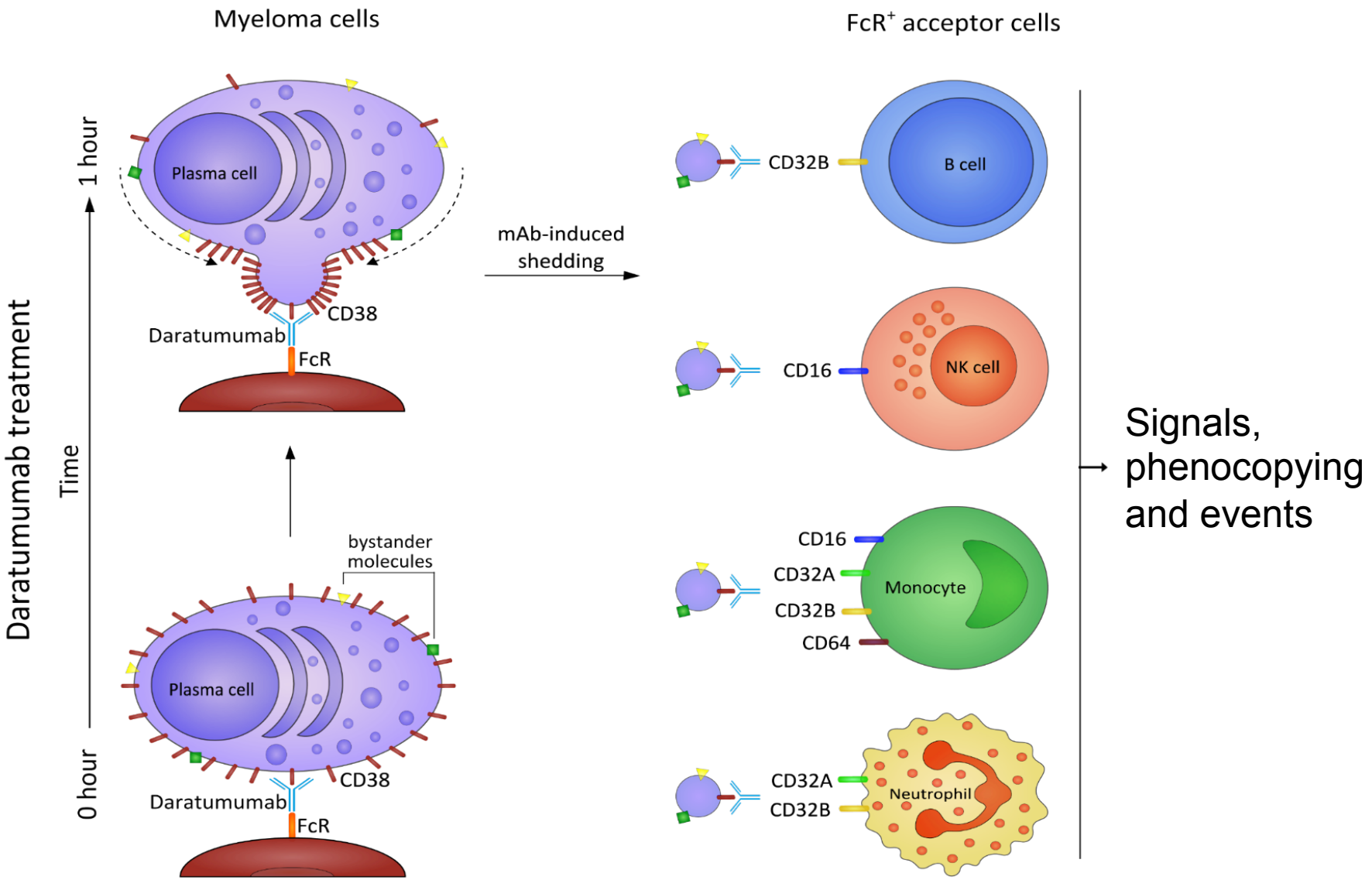
M.Giuliani, B. Janji and G. Berchem, Oncotarget, 2017

Human IgG receptor expression pattern

Name	FcγRI	FcγRIIA	FcγRIIB	FcγRIIC[¤]	FcγRIIIA	FcγRIIIB	FcRn
CD	CD64	CD32A	CD32B	CD32C	CD16A	CD16B	-
							
B cell	-	-	+	-	-	-	-
T cell	-	-	-	-	-	-	-
NK cell	-	-	-[#]	+[¤]	+	-	-
Mono/Macro	+	+	+/-	+[¤]	+	-	+
Neutrophil	(+)	+	+/-	+[¤]	-	+	+
Dendritic Cell[§]	+	+	+	-	-	-	+
Basophil	-	+	+	-	-	+/-	-
Mast cell	(+)	+	-	-	-	-	NA
Eosinophil	-	+	-	-	-	-	-
Platelet	-	+	-	-	-	-	NA
Endothelium	-	-	-	-	-	-	+

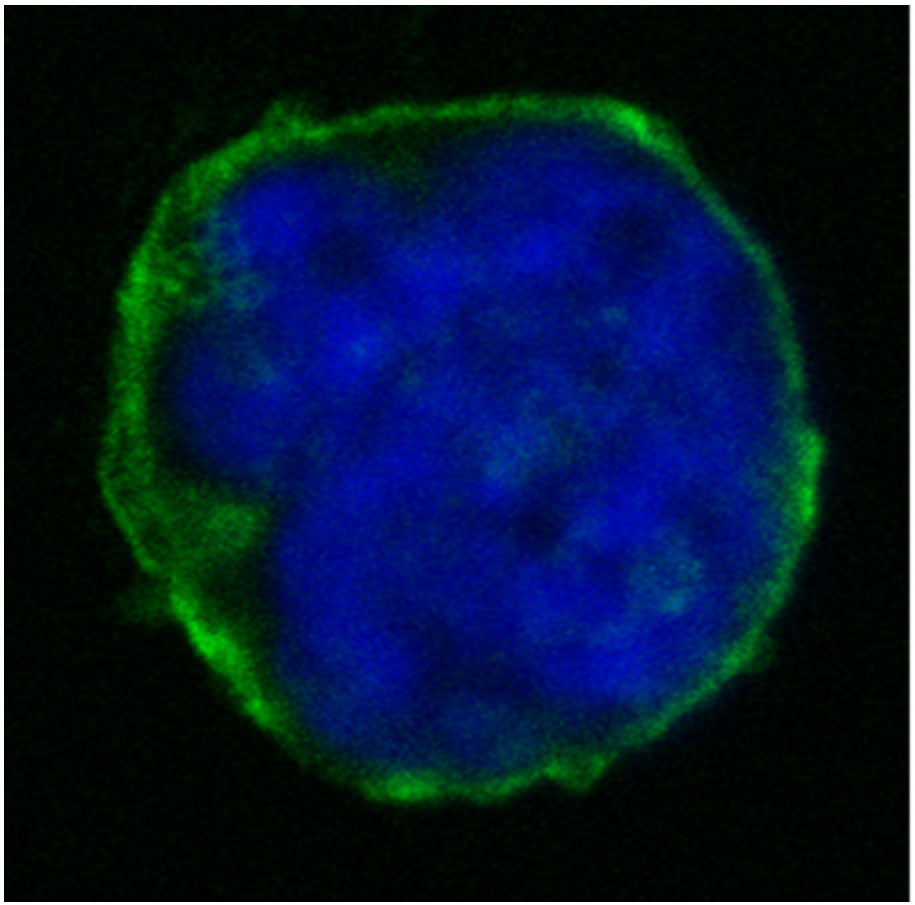
Gillis C. et al, Frontiers Immunol. (2014)

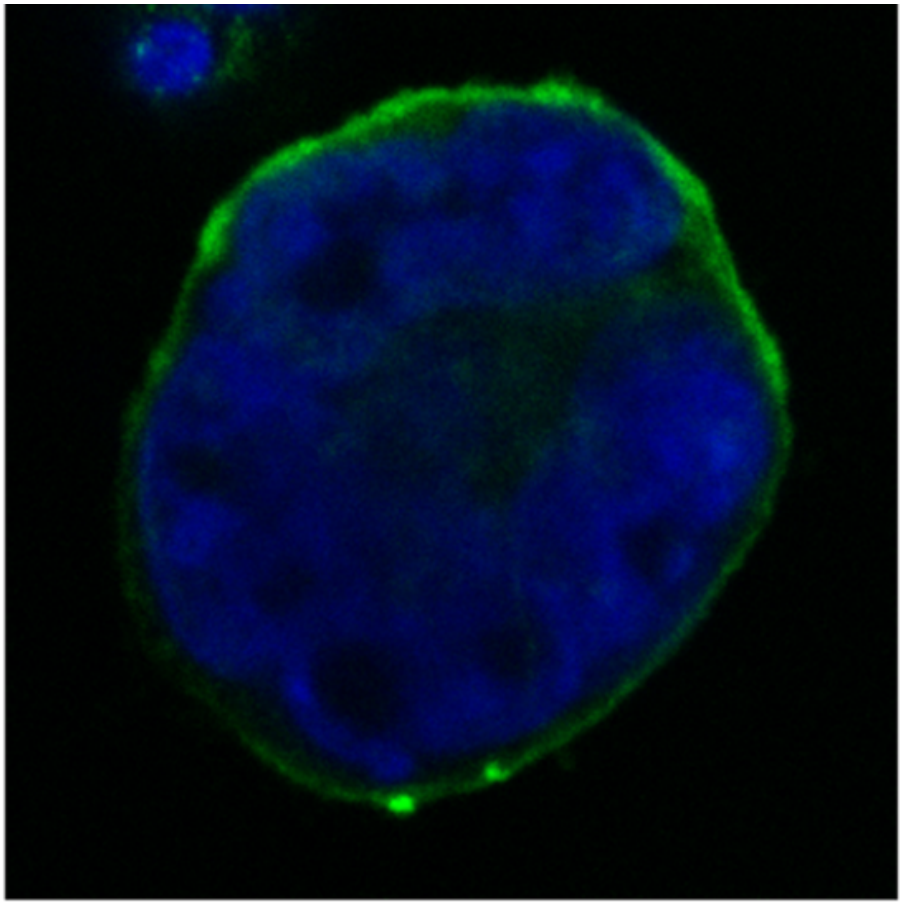
In vivo events when a mAb reaches its myeloma target



A. Chillemi *et al.* Cells. 2015 Sep 17;4(3):520-37.

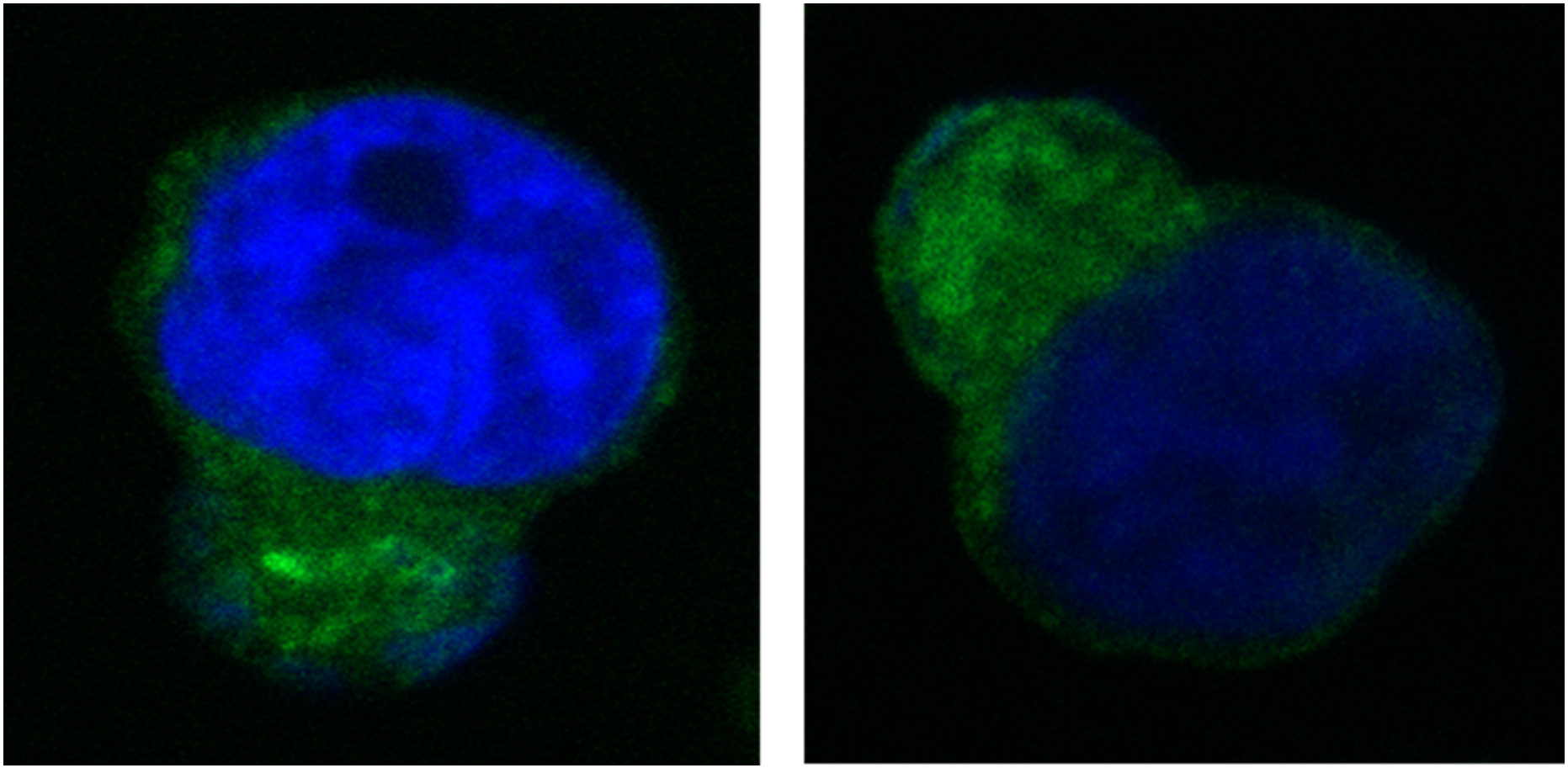
Confocal microscopy analysis of CD38/DARA interaction (4°C) on a relapsed myeloma





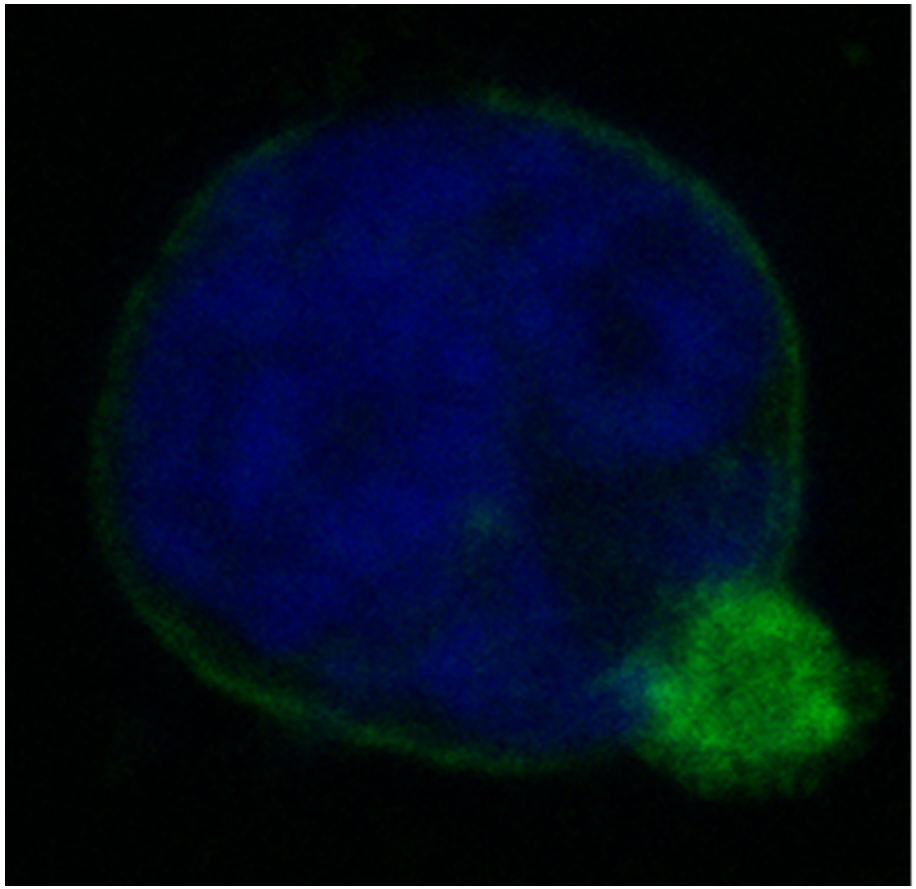
A. Chillemi *et al.* (in preparation, 2017)

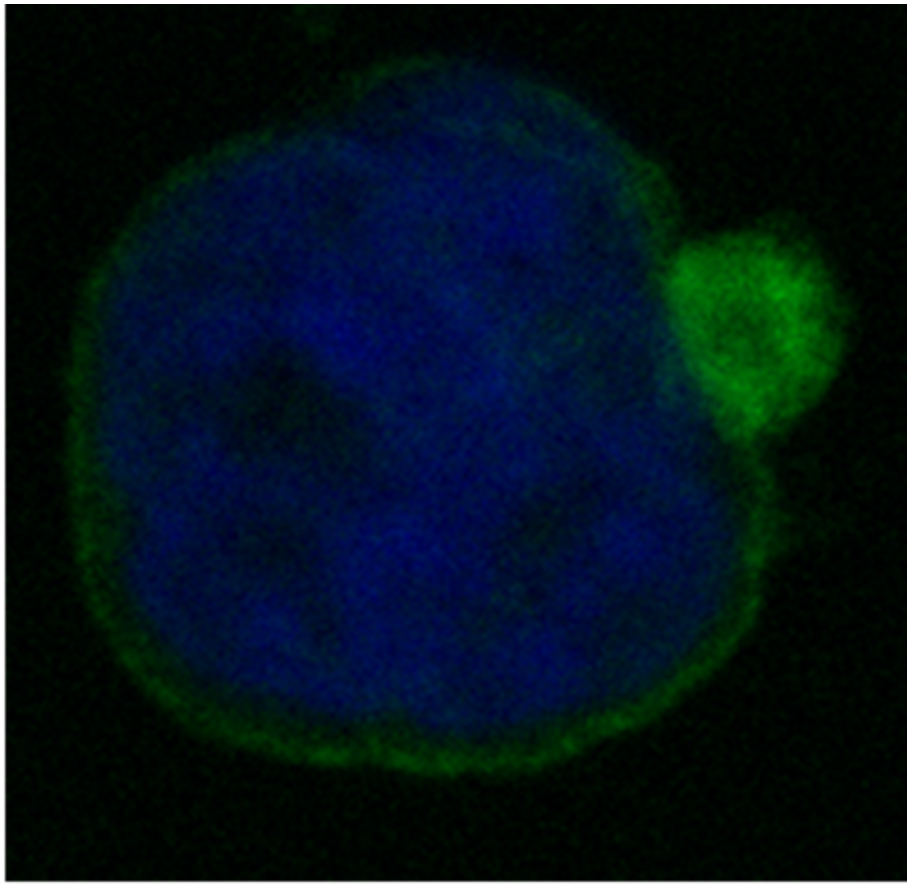
Confocal microscopy analysis of CD38/DARA interaction (37 °C, 3 h) on a myeloma at diagnosis



A. Chillemi *et al.* (in preparation, 2017)

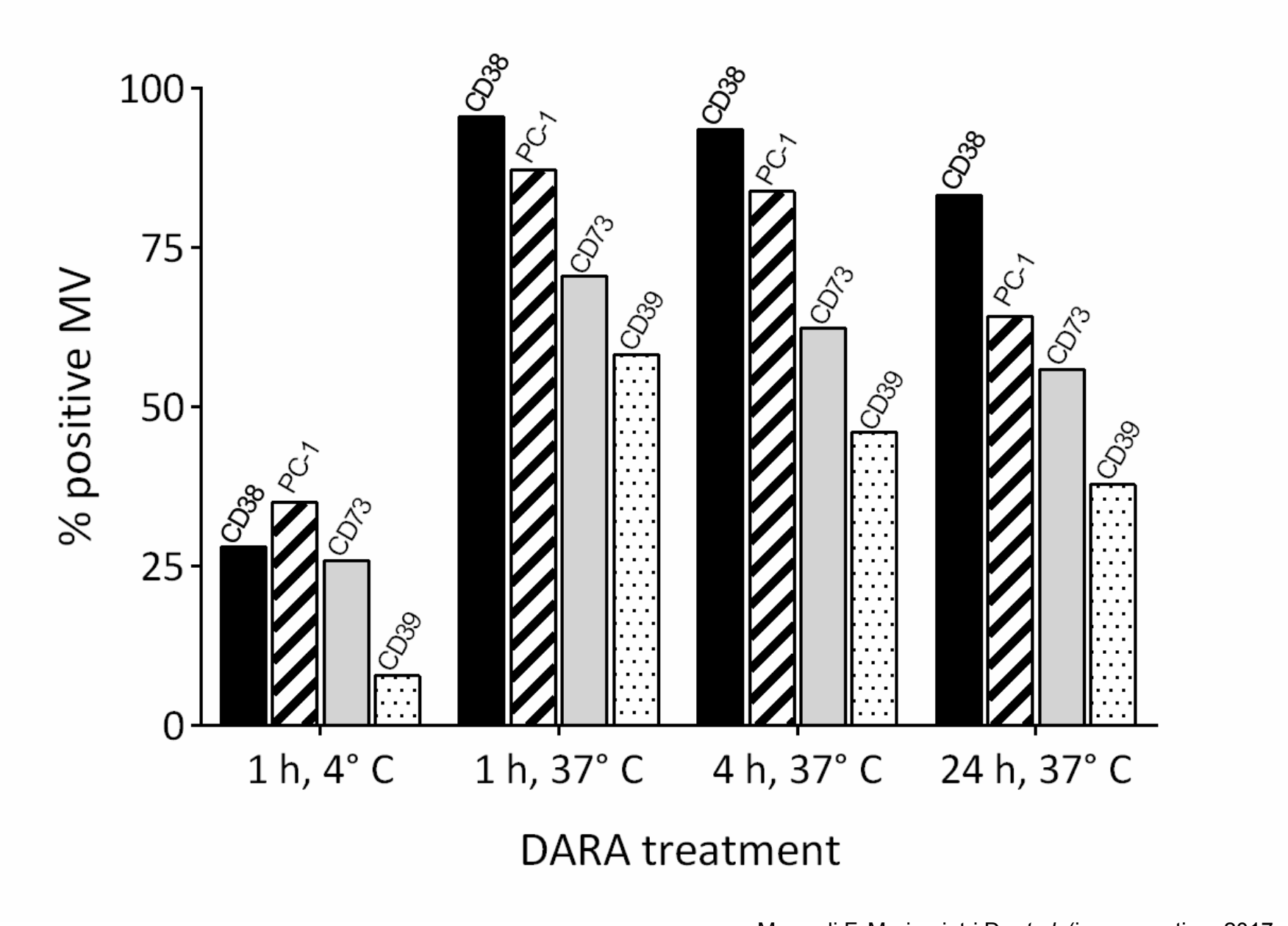
Confocal microscopy analysis of CD38/DARA interaction (37 °C, 2 h) on a myeloma at diagnosis





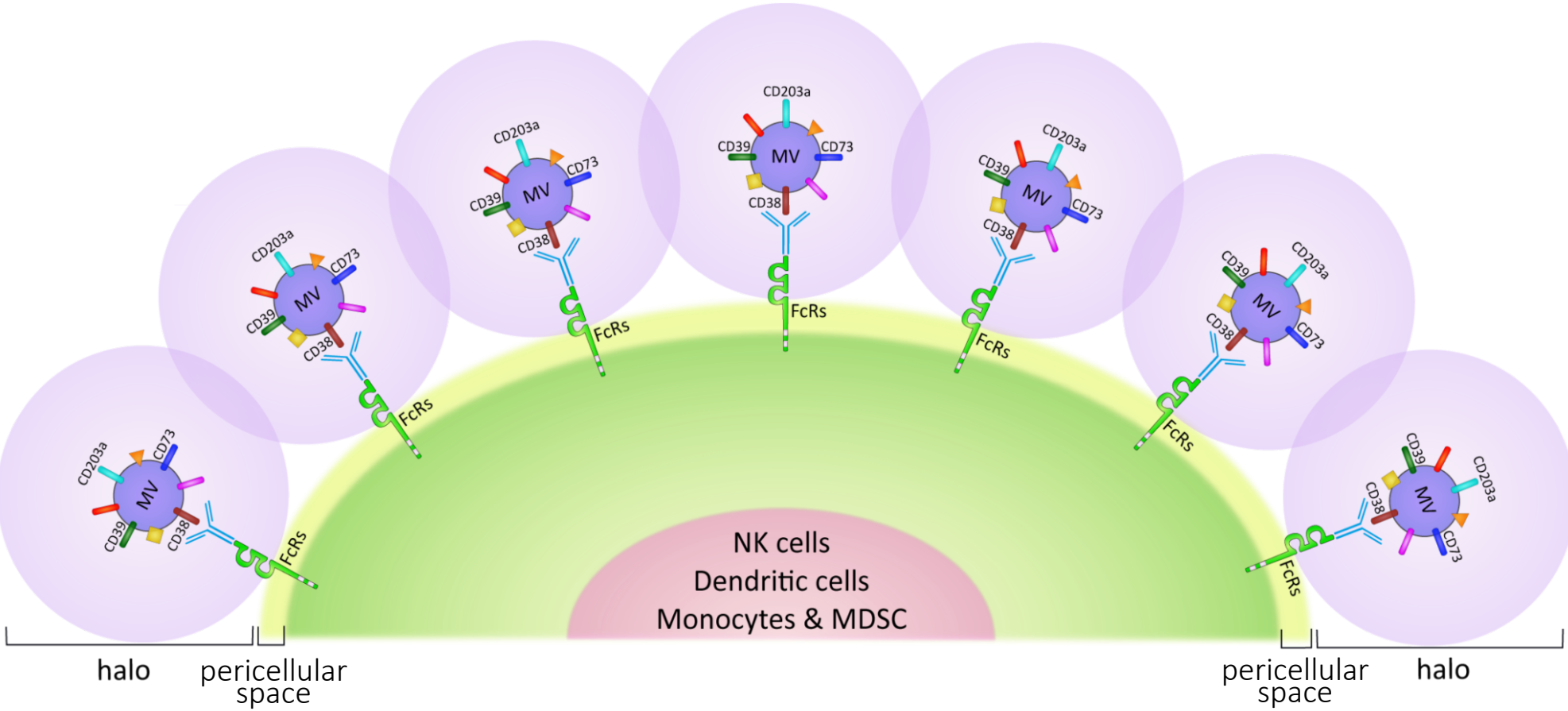
A. Chillemi *et al.* (in preparation, 2017)

MV phenotype from MM after treatment with anti-CD38 mAbs

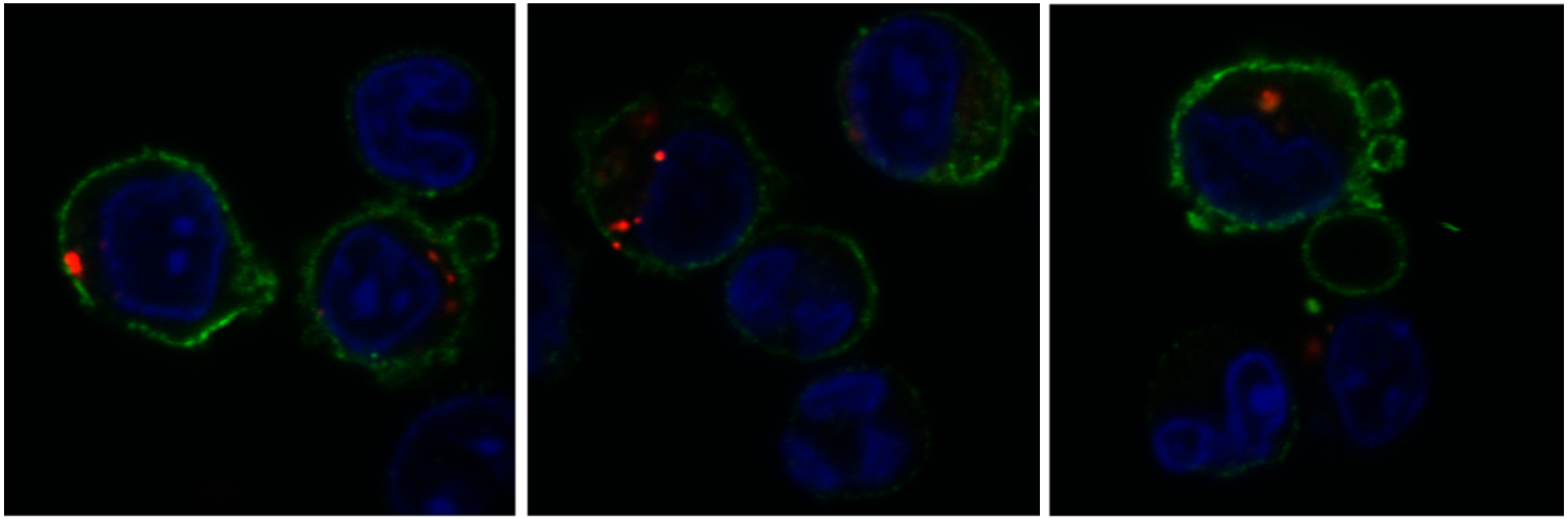


Morandi F, Marimpietri D, *et al.* (in preparation, 2017)

Enzymatic halo and MV define a pericellular space



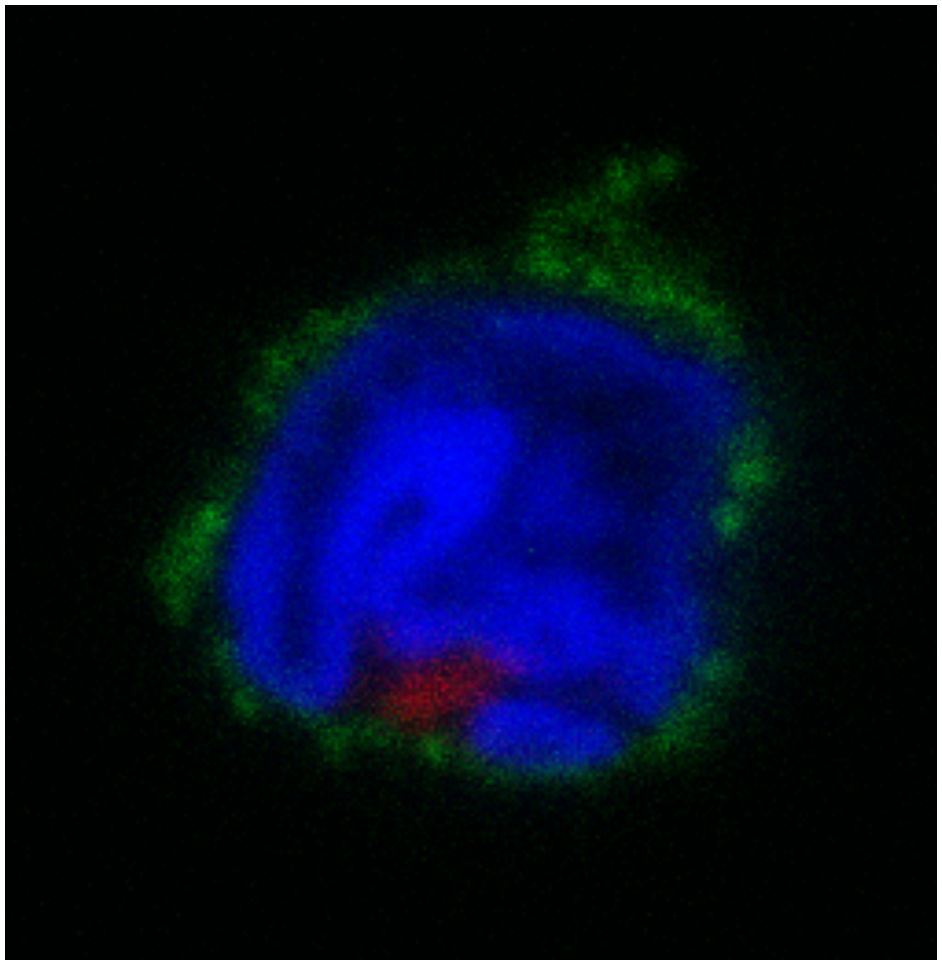
Whither MV from multiple myeloma:
2) Entering MDSC ($CD15^+/CD33^+/CD11b^+$)

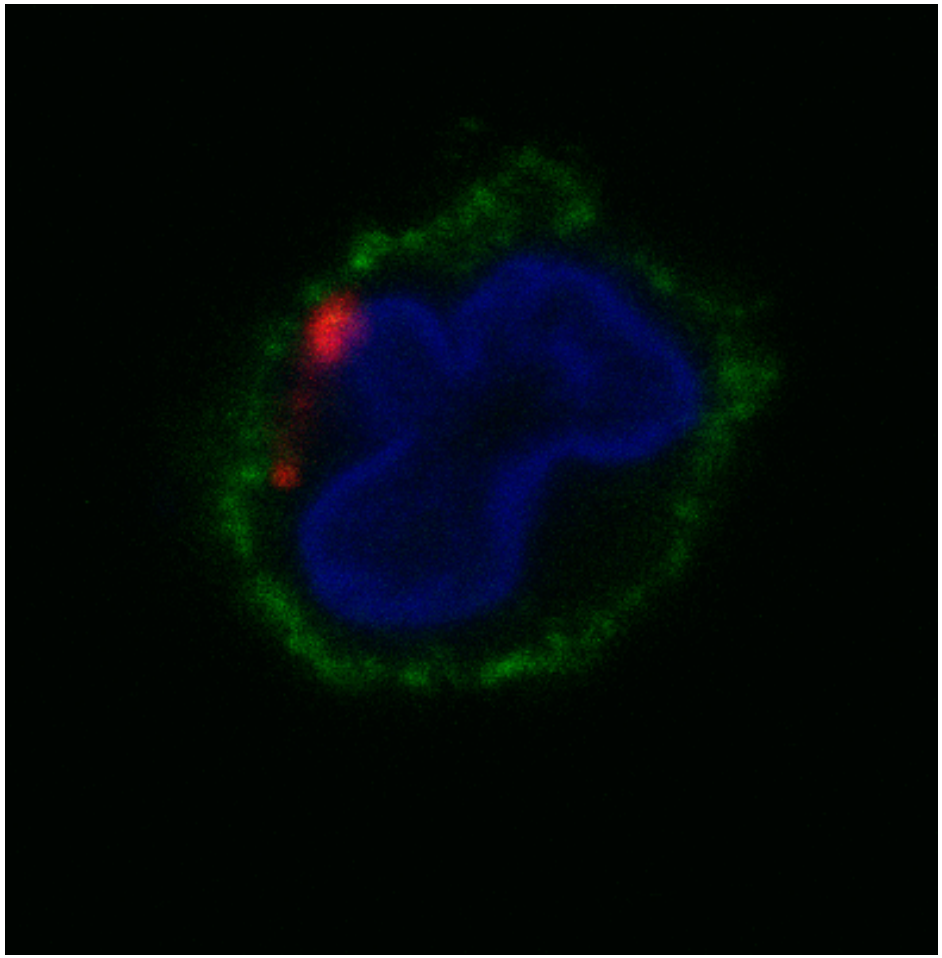


Green = anti-CD14 mAb plus anti-mouse IgG-Alexa 488
Red = MV labeled with1,1'-Dioctadecyl-3,3,3',3'-tetramethylindodicarbocyanine 4-chlorobenzenesulfonate (DiD)
Blue = 4',6-Diamidino-2-Phenylindole (DAPI)

A. Chillemi, B. Castella *et al.* (in preparation, 2017)

Whither MV from multiple myeloma: 3) Entering NK cells ($CD16^{+}$)





Green = anti-CD16 mAb plus anti-mouse IgG-Alexa 488
Red = MV labeled with1,1'-Dioctadecyl-3,3,3',3'-tetramethylindodicarbocyanine 4-chlorobenzenesulfonate (DiD)
Blue = 4',6-Diamidino-2-Phenylindole (DAPI)

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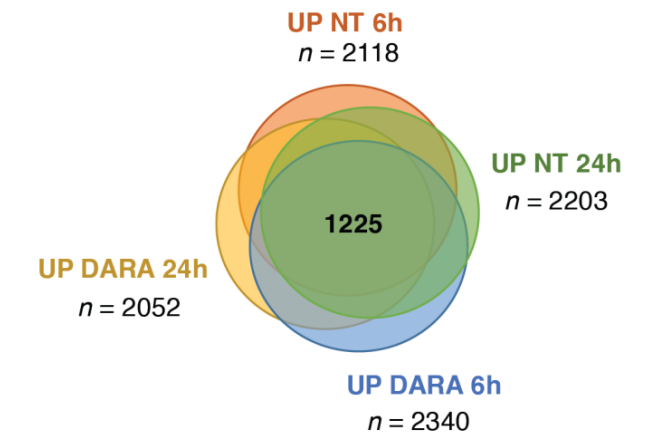
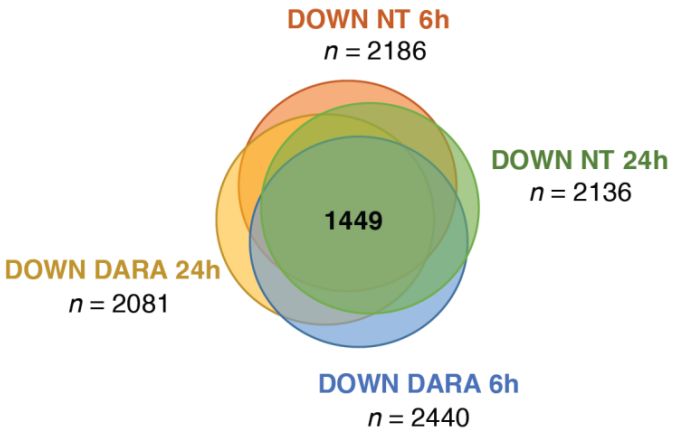
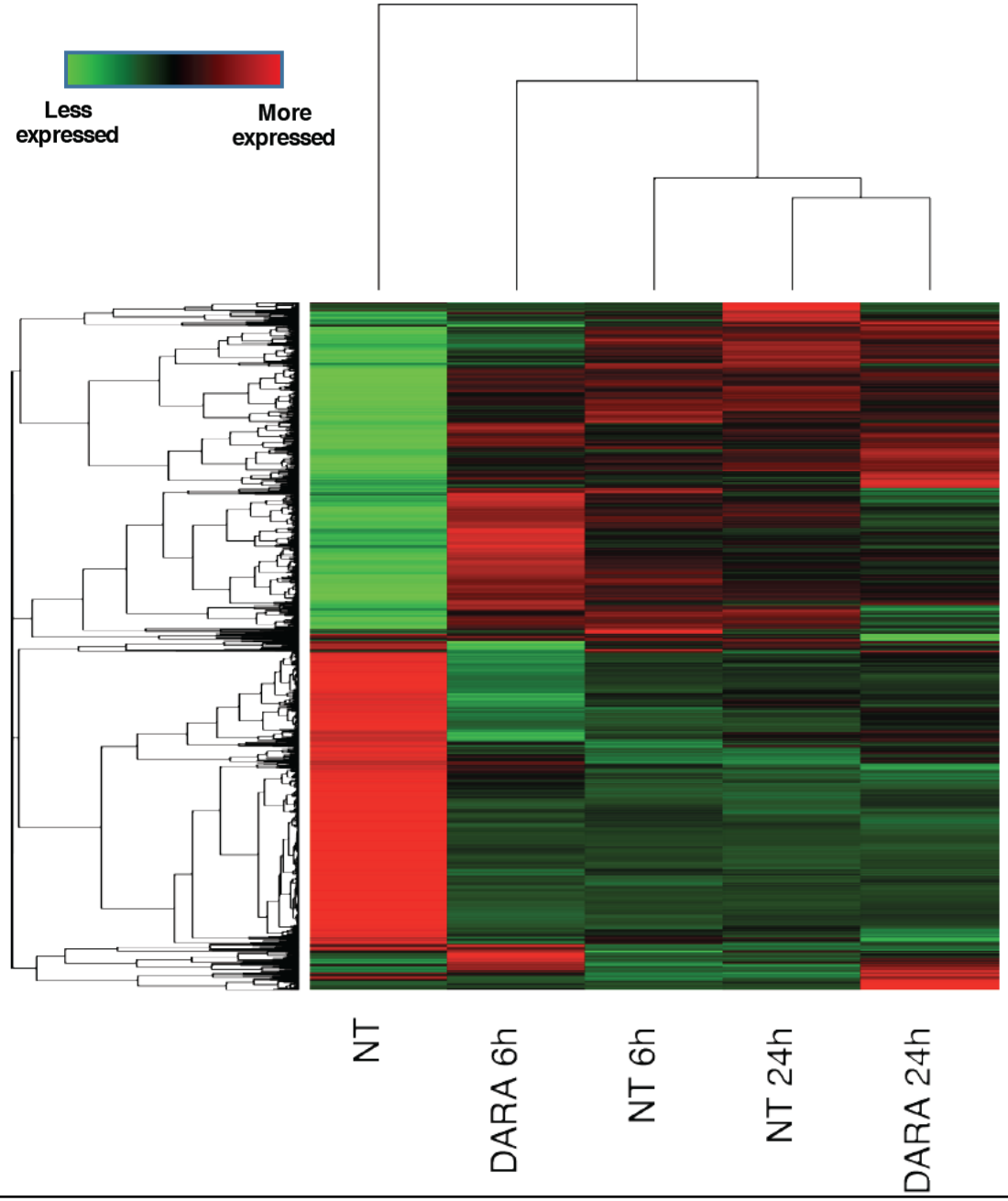
Whither MV from multiple myeloma:
4) Molecular effects observed on NK cells ($CD16^{+}/CD56^{+}$)







Questions to be answered

Can anti-CD38 mAbs be active in various phases of treatment (induction, consolidation, maintenance)?

May anti-CD38 mAbs influence escape strategies of myeloma cells?

Can anti-CD38 mAb resistance be predicted?

Adapted from Raje & Longo. N Engl J Med 2015 Aug 26 [Epub]

THE UNIVERSITY OF TEXAS
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CD38 as a novel immune checkpoint and mechanism of resistance to the blockade of the PD-1/PD-L1 axis

Limo Chen, PhD

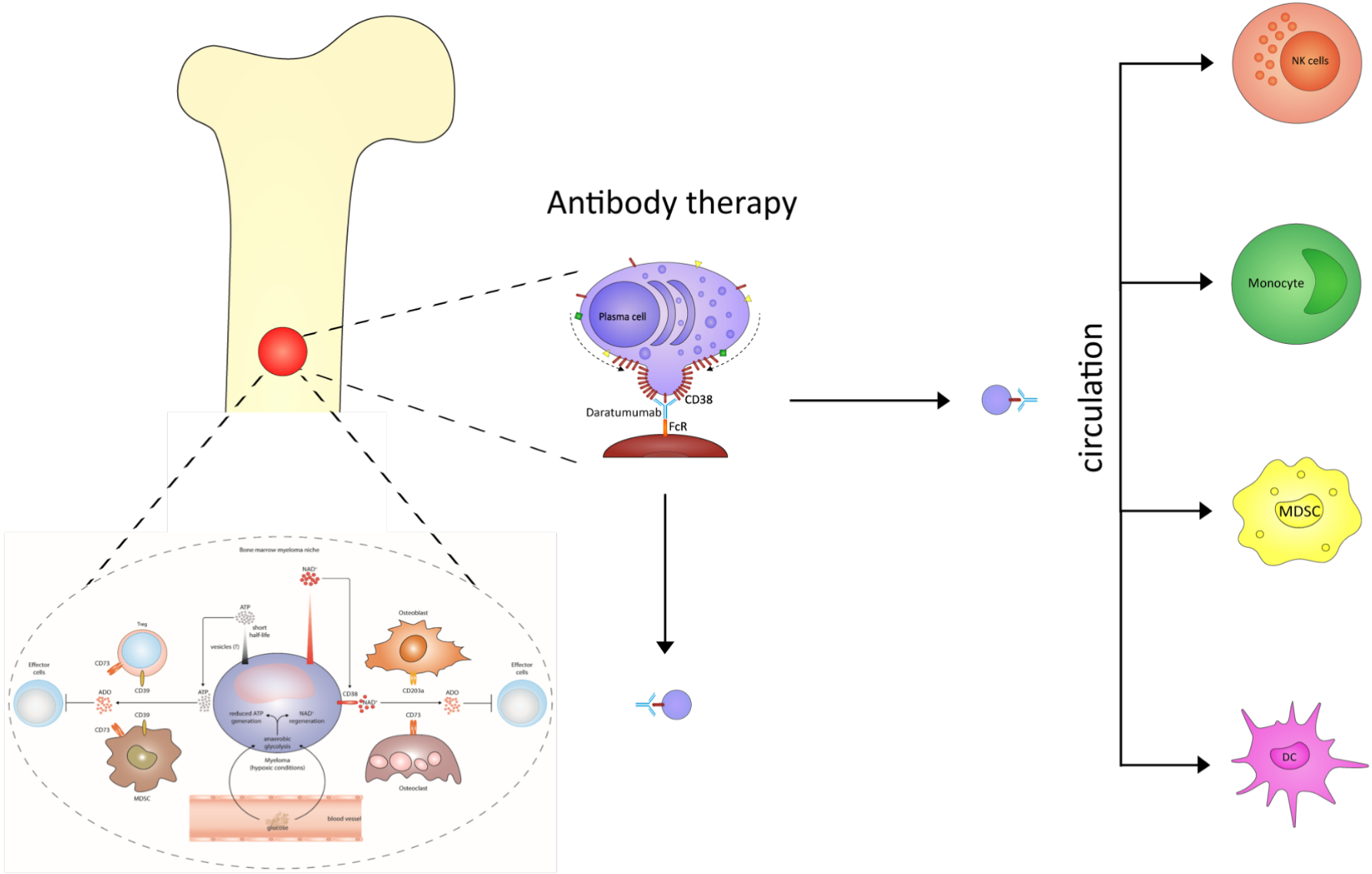
(Gibbons Lab)

(Department of Thoracic/Head and Neck Medical Oncology)

ASCO-SITC Clinical Immuno-Oncology Symposium

February 23-25, 2017, Orlando, FL

Soluble and particulate communications between myeloma and cells *in situ* and after antibody treatment: a hypothesis



A. Chillemi *et al.*, 2017, in preparation

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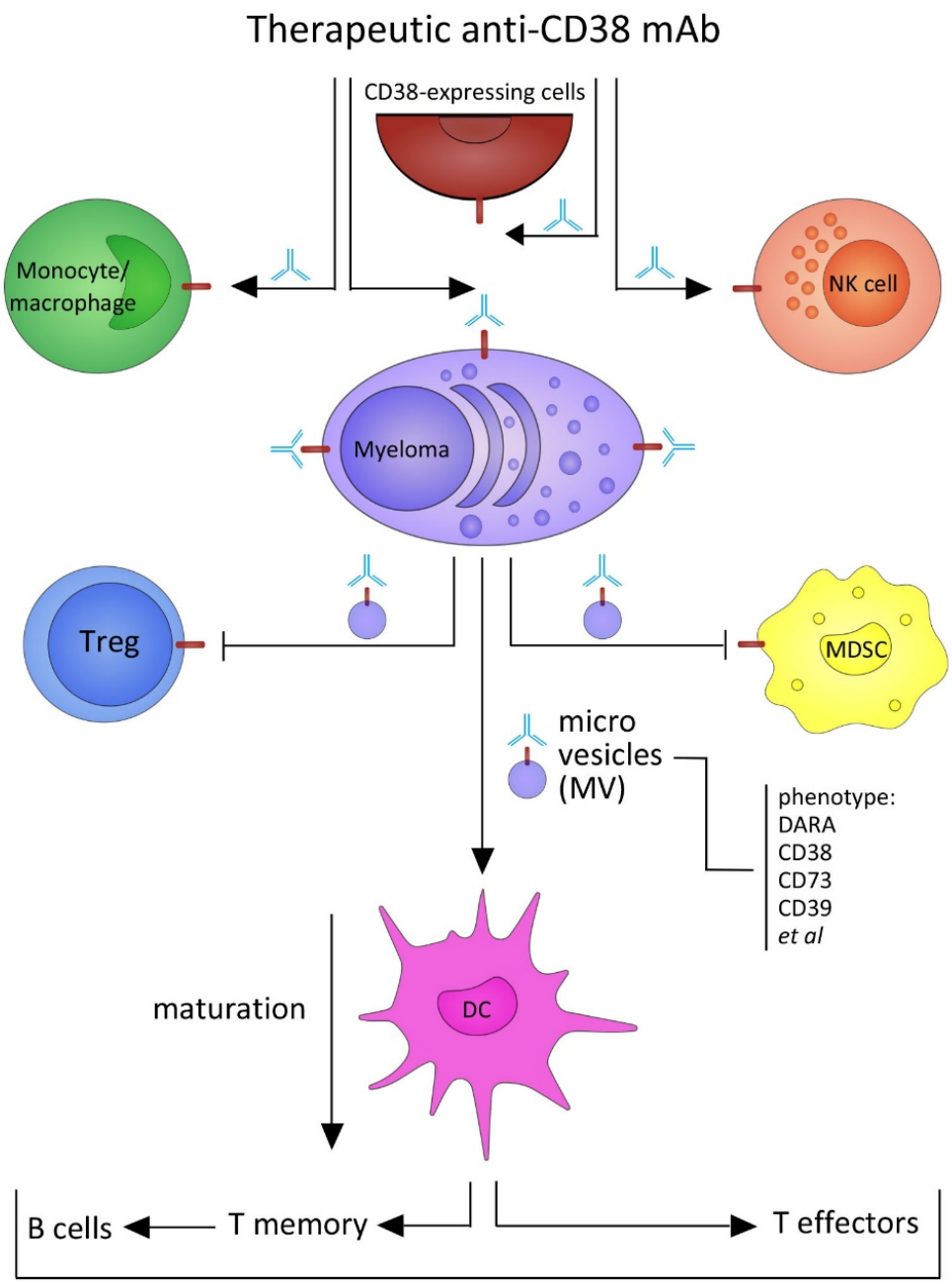
CD38 in the time of therapeutic mAbs

Proposals



Myeloma niche:
Adenosine levels

Biological fluids:
Quality of circulating MV

Biological fluids:
Vaccinal effects