Idiotypic vaccination: why we have failed ~~20~~ 25 years ago

Massimo Massaia

SC Ematologia - AO S. Croce e Carle – Cuneo, Italy

Laboratorio di Immunologia dei Tumori del Sangue, CIRBM Torino, Italy

1 st Cuneo City ImmunoTherapy Conference (CCITC)

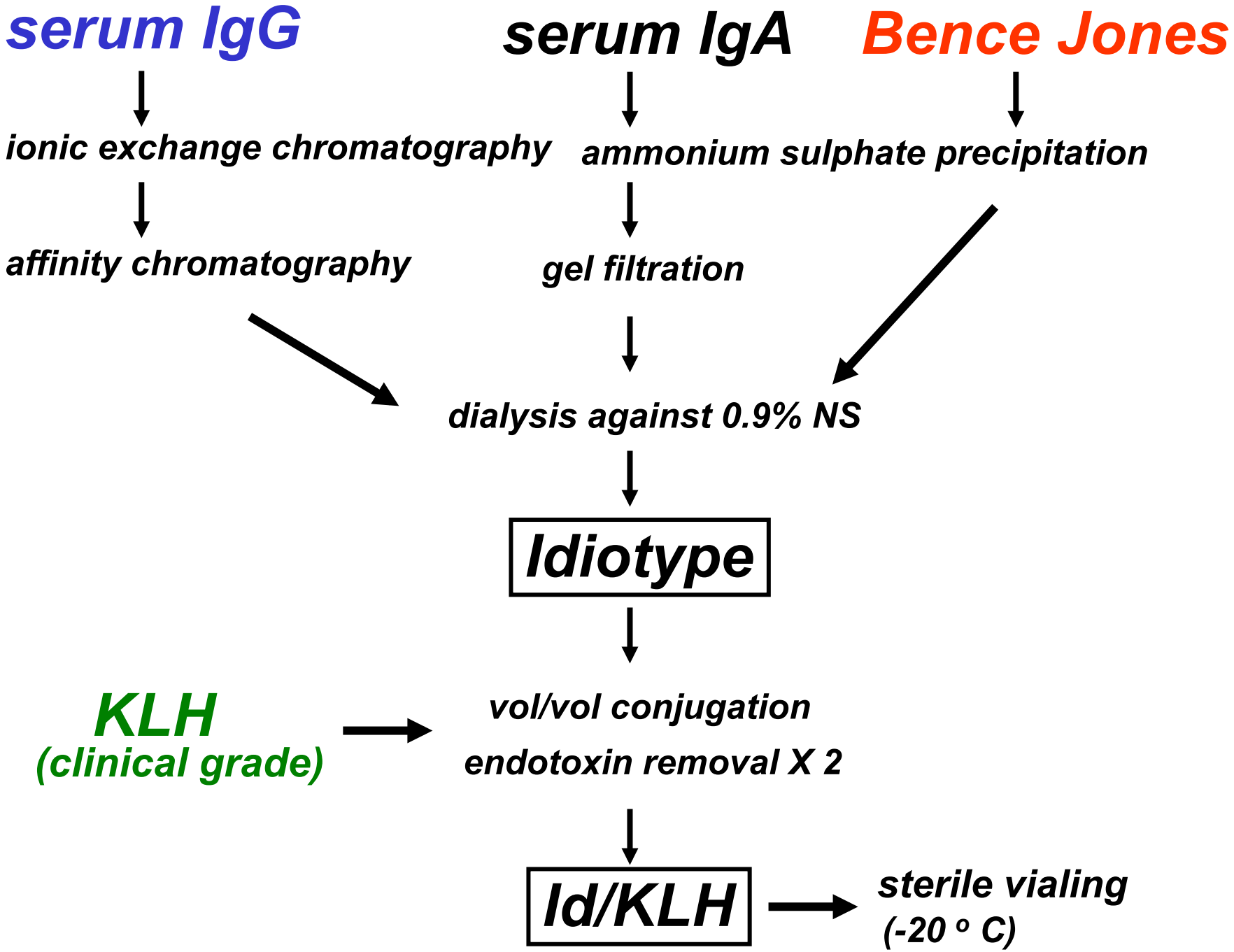
Immunotherapy in Hematological Malignancies 2018

Cuneo, May 17-19, 2018

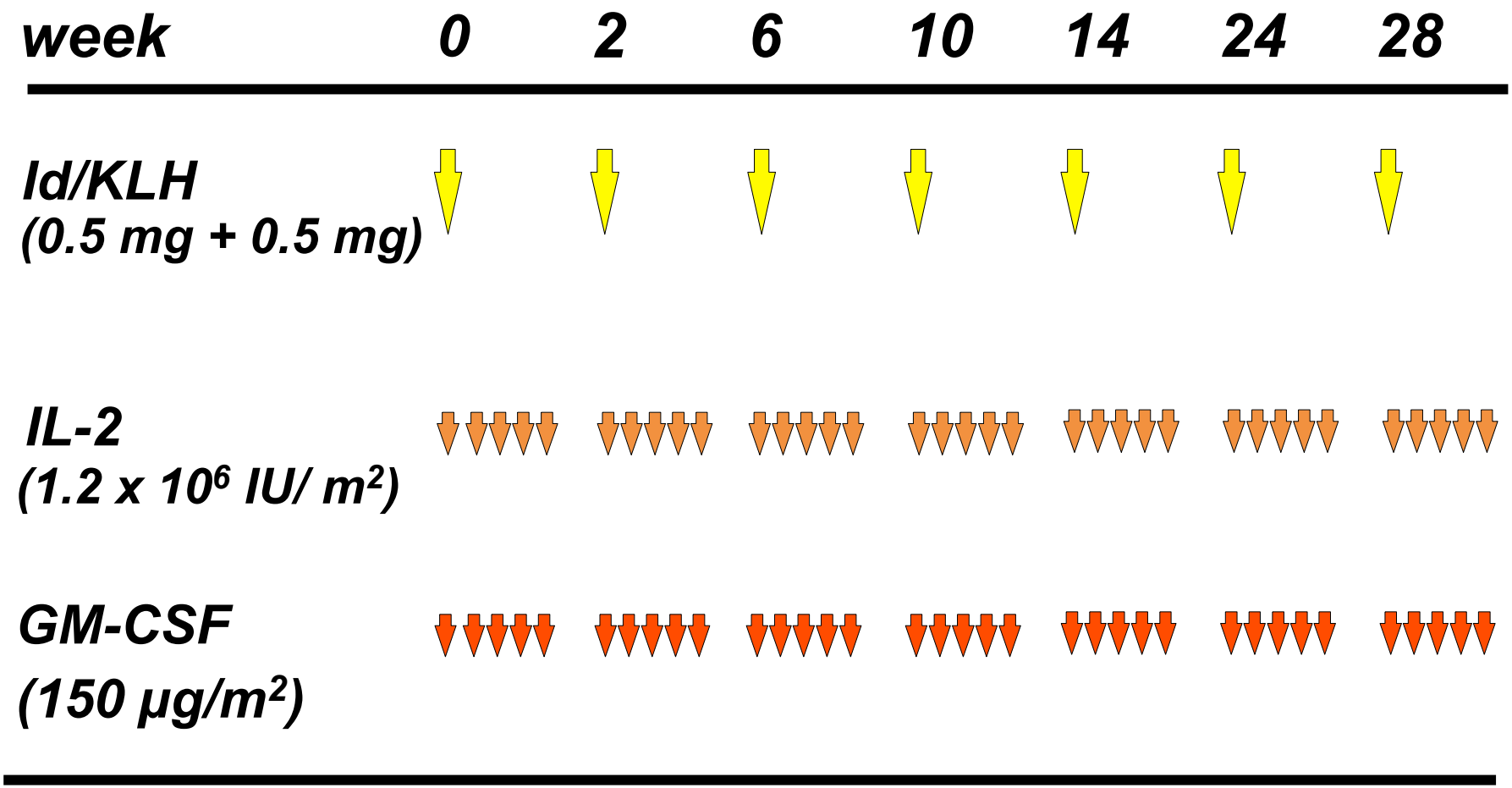
AO S.Croce e Carle
Cuneo

Università di Torino
MBC
Molecular Biotechnology Center

CeRMS
Centro di Ricerca in Medicina Sperimentale


serum IgG
serum IgA
Bence Jones
ionic exchange chromatography
ammonium sulphate precipitation
affinity chromatography
gel filtration
dialysis against 0.9% NS
Idiotype
KLH
(clinical grade)
vol/vol conjugation
endotoxin removal X 2
Id/KLH
sterile vialing
(-20 º C)

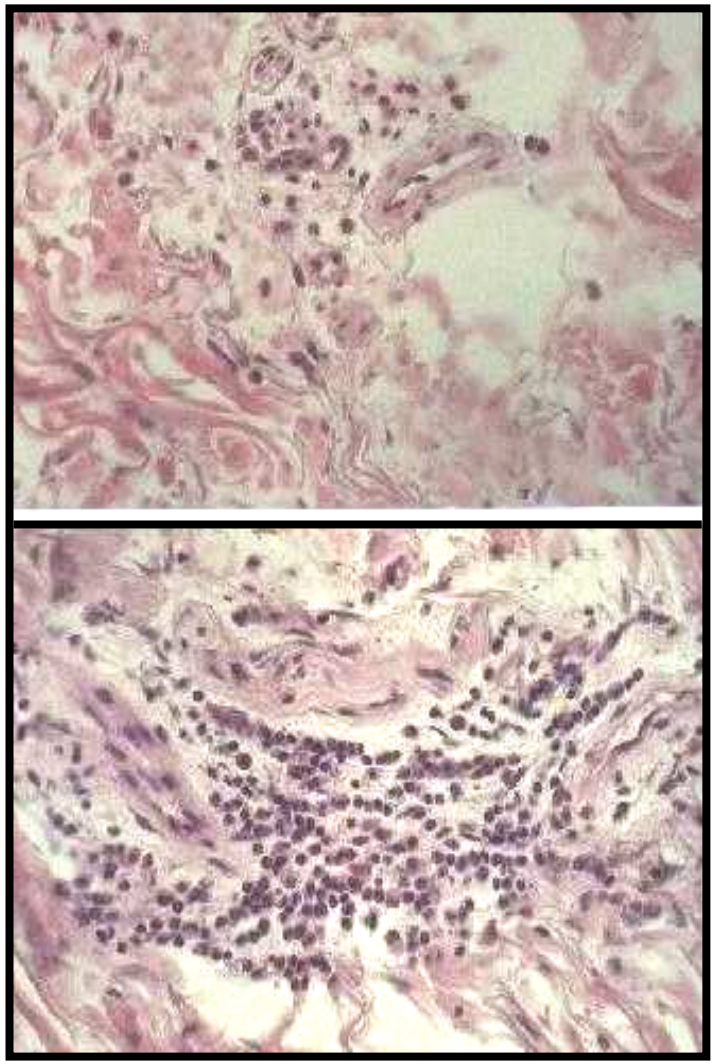
Protocol 9401



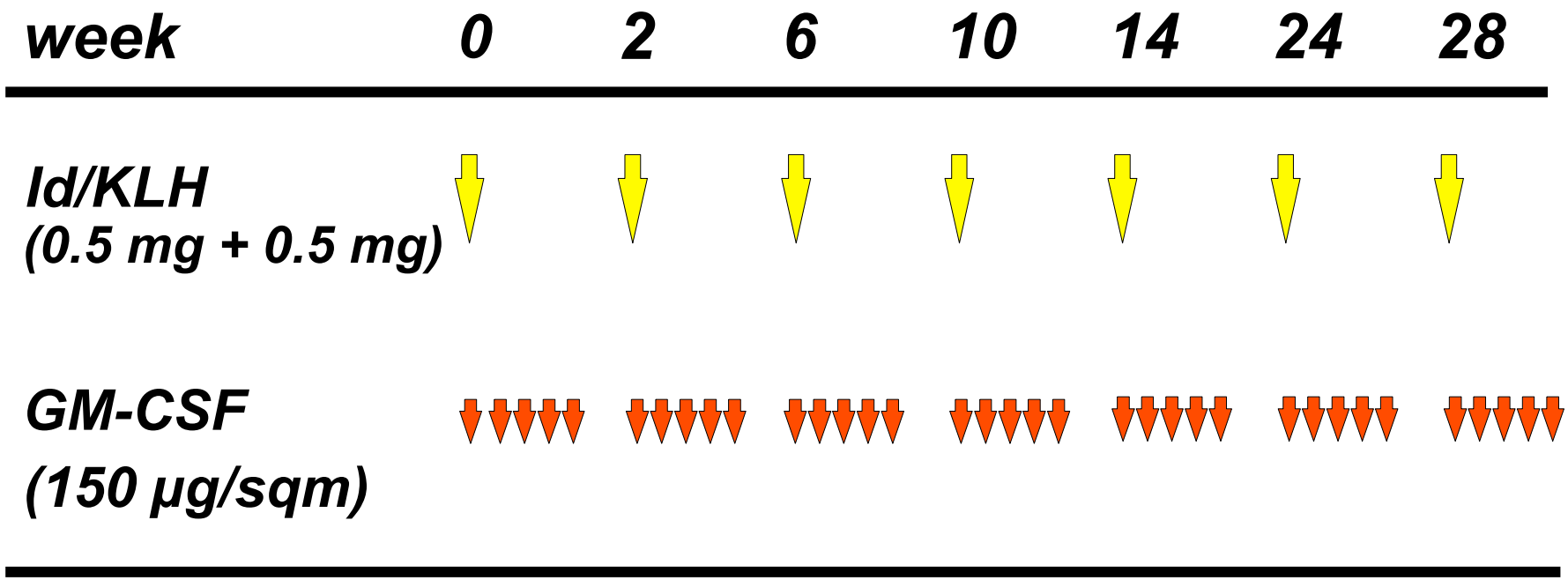
DTH responses in MM receiving Id/KLH conjugates

IL-2
(1.2 x 10^6 IU/sqm for 5 days)

GM-CSF
(150 μg/sqm for 5 days)

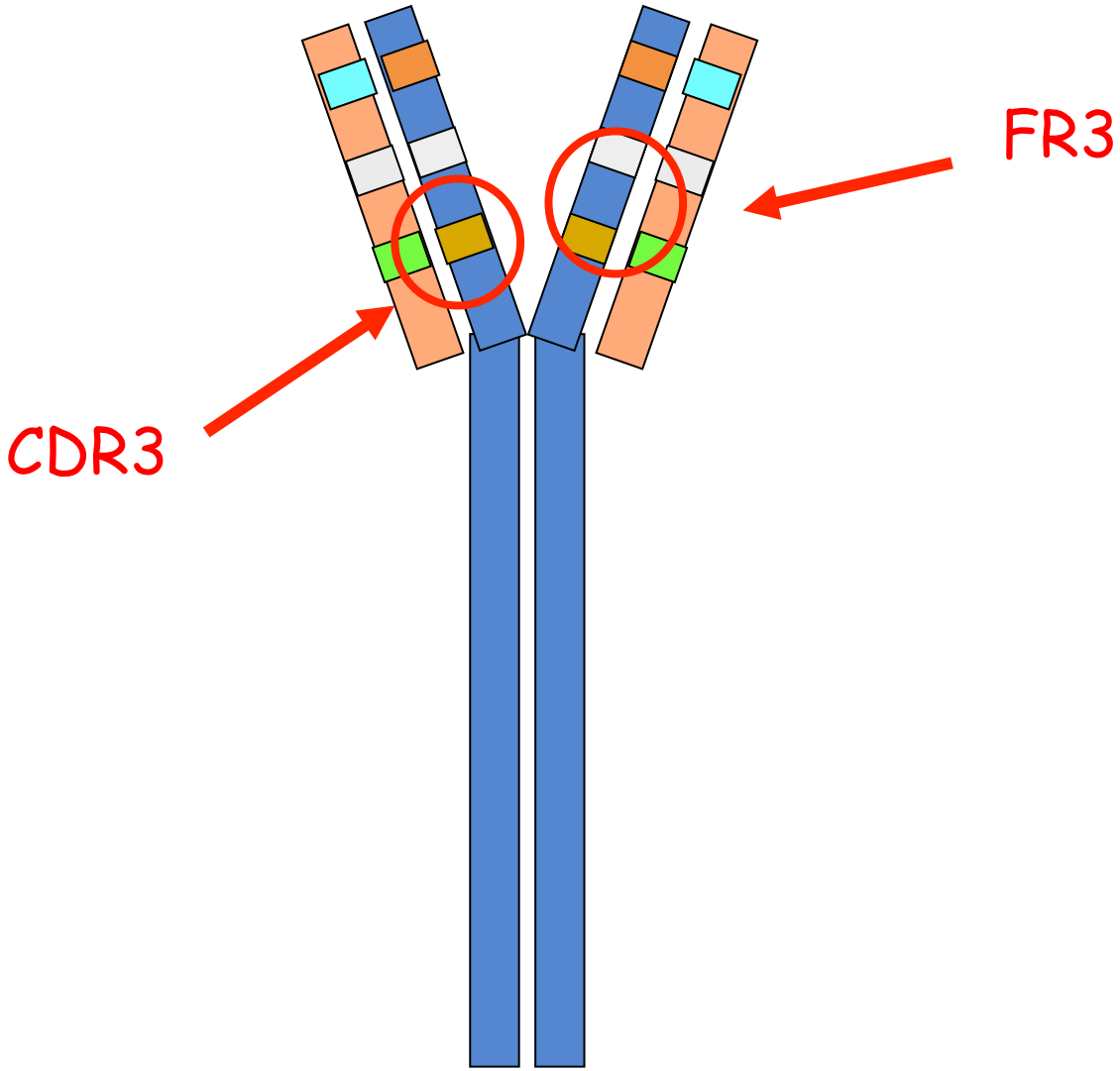


Protocol 9402



- 15 MM in first remission after HDS and PBPC infusion;

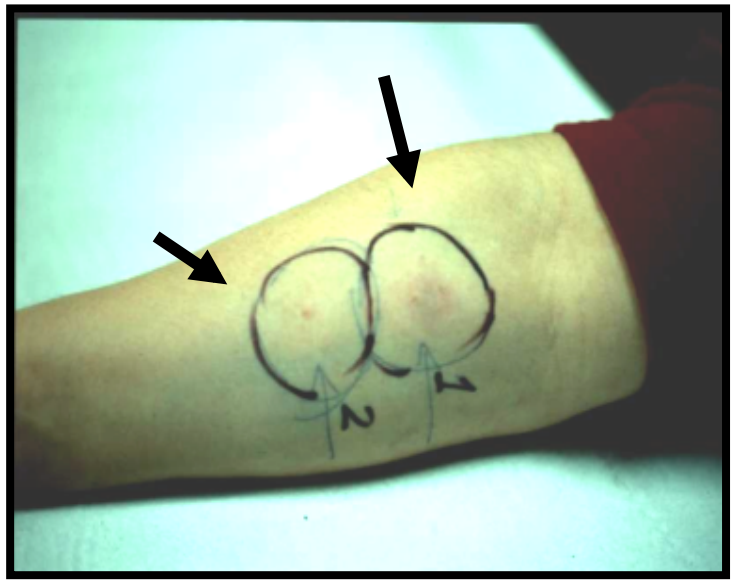
tumor-derived immunoglobulin



DTH responses in MM receiving Id/KLH conjugates

CDR3-derived peptide (1)

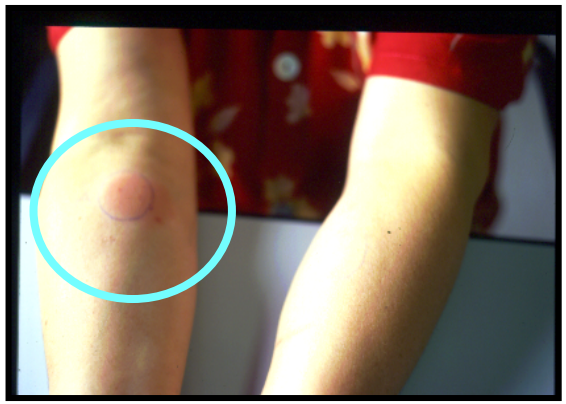
FR3-derived peptide (2)



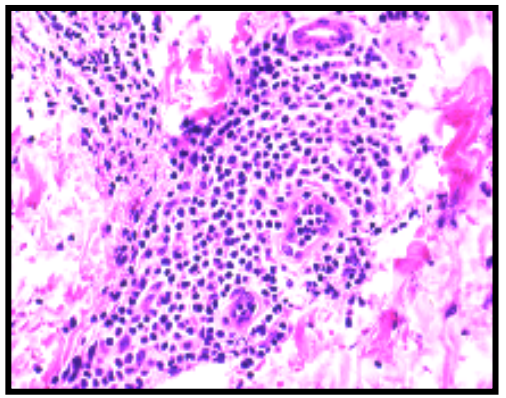
Massaia M et al., *Blood*. 1999 Jul 15;94(2):673-83.

Late DTH responses

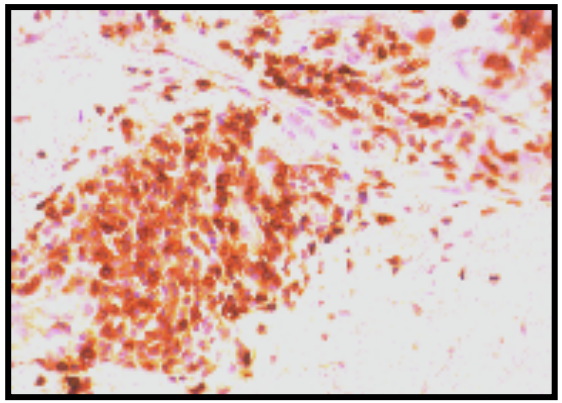
post-vax



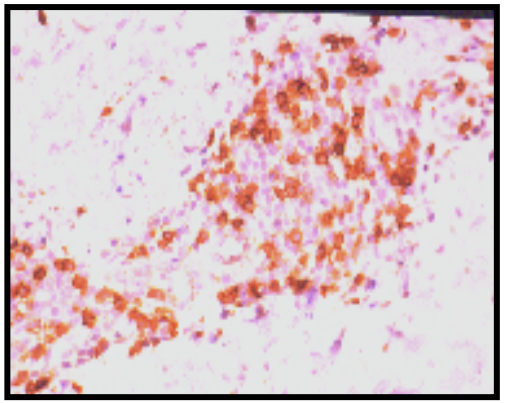
lymph.



CD4



CD8



Massaia M et al., *Blood*. 1999 Jul 15;94(2):673-83.

Table 2. Antibody responses to vaccine components

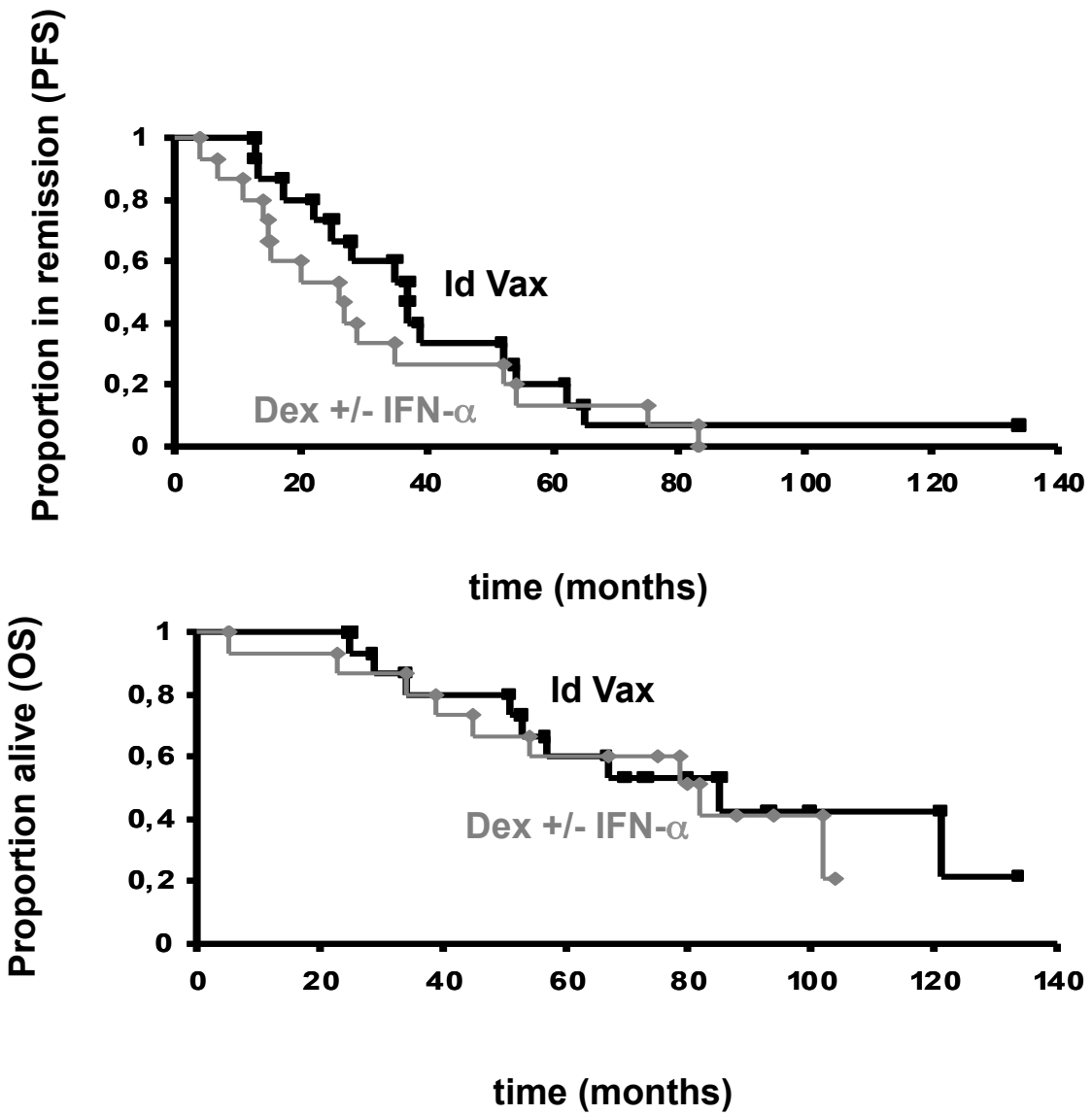
ant-KLH			anti-Id+[a]			anti-Id-[b]			Anti-GM-CSF		
IgM	IgG	IgE	IgM	IgG	IgE	IgM	IgG	IgE	IgM	IgG	IgE
9/10[c]	9/10	5/15	0/15	3/15	5/15	0/15	3/15	4/15	nd[d]	3/15	nd

[a] autologous Id

[b] isotype-related allogeneic Id

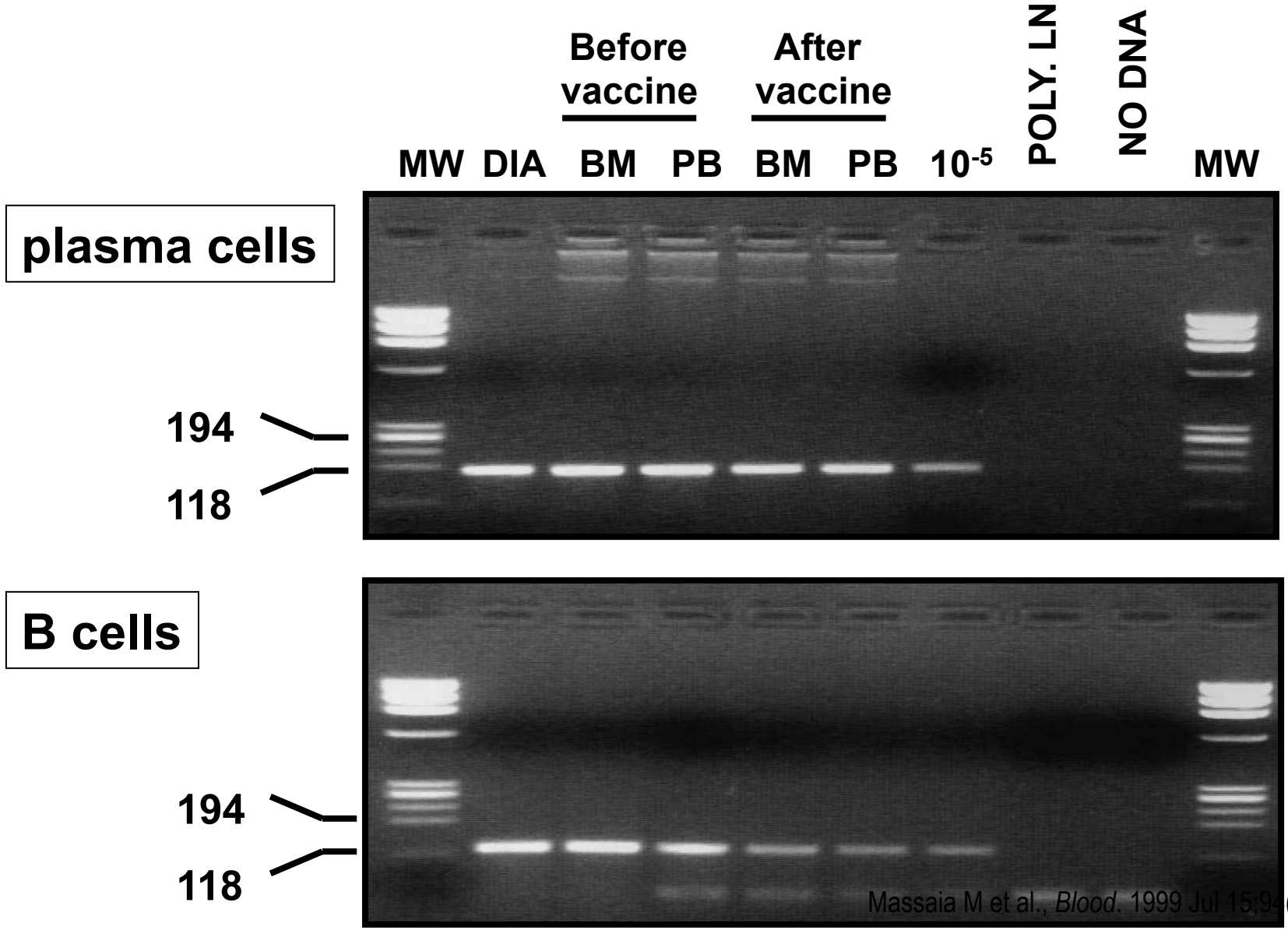
[c] positive/tested patients

[d] not done



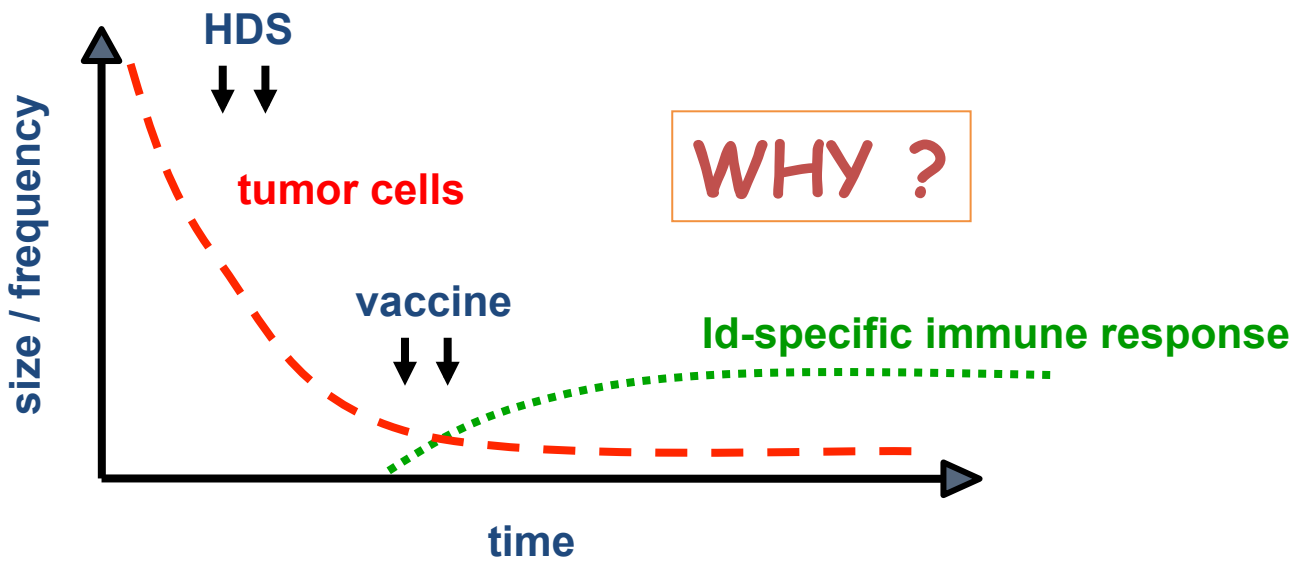
Coscia M et al., *Leukemia*. 2004 Jan;18(1):139-45.

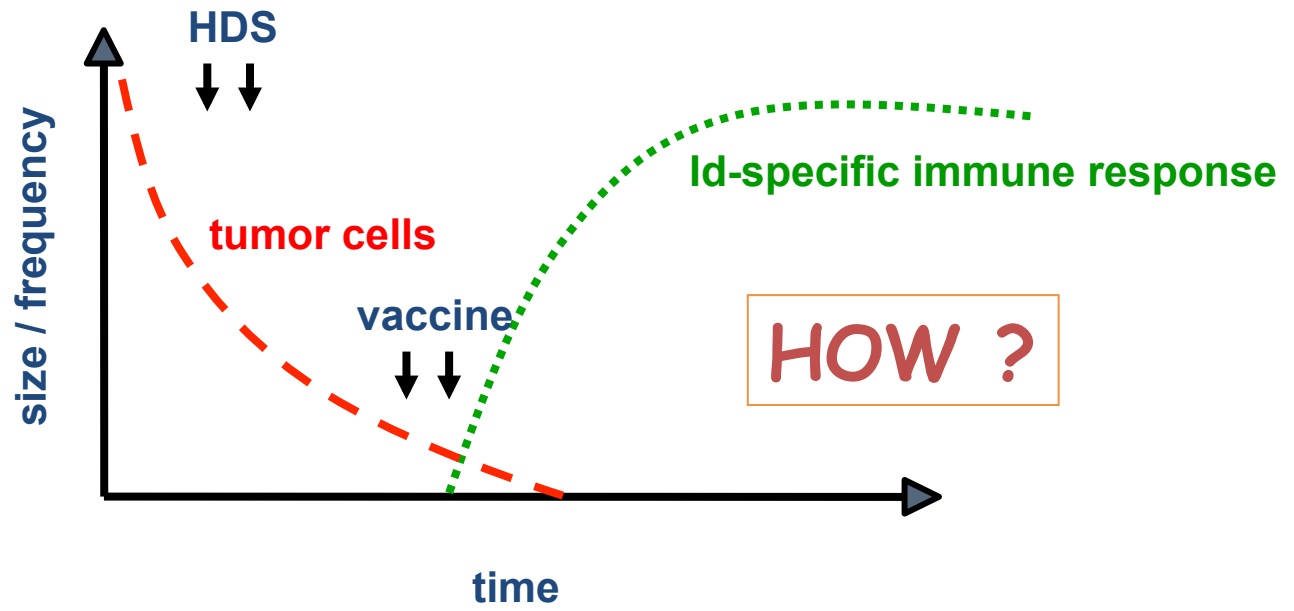
minimal residual disease detection



Massaia M et al., *Blood*. 1999 Jul 15;94(2):673-83.

Coscia M et al., *Leukemia*. 2004 Jan;18(1):139-45.


HDS
tumor cells
vaccine
Id-specific immune response
size / frequency
time
WHY ?


HDS
tumor cells
vaccine
Id-specific immune response
size / frequency
time
HOW ?

Bullet points:

- Better TAAs than Id?

- Early & persistent immune suppressive TME commitment

- Redundancy of ICP/ICP-L pairs in TME

- Is hot or cold the TME in MM (rem vs dia etc)?

Idiotype

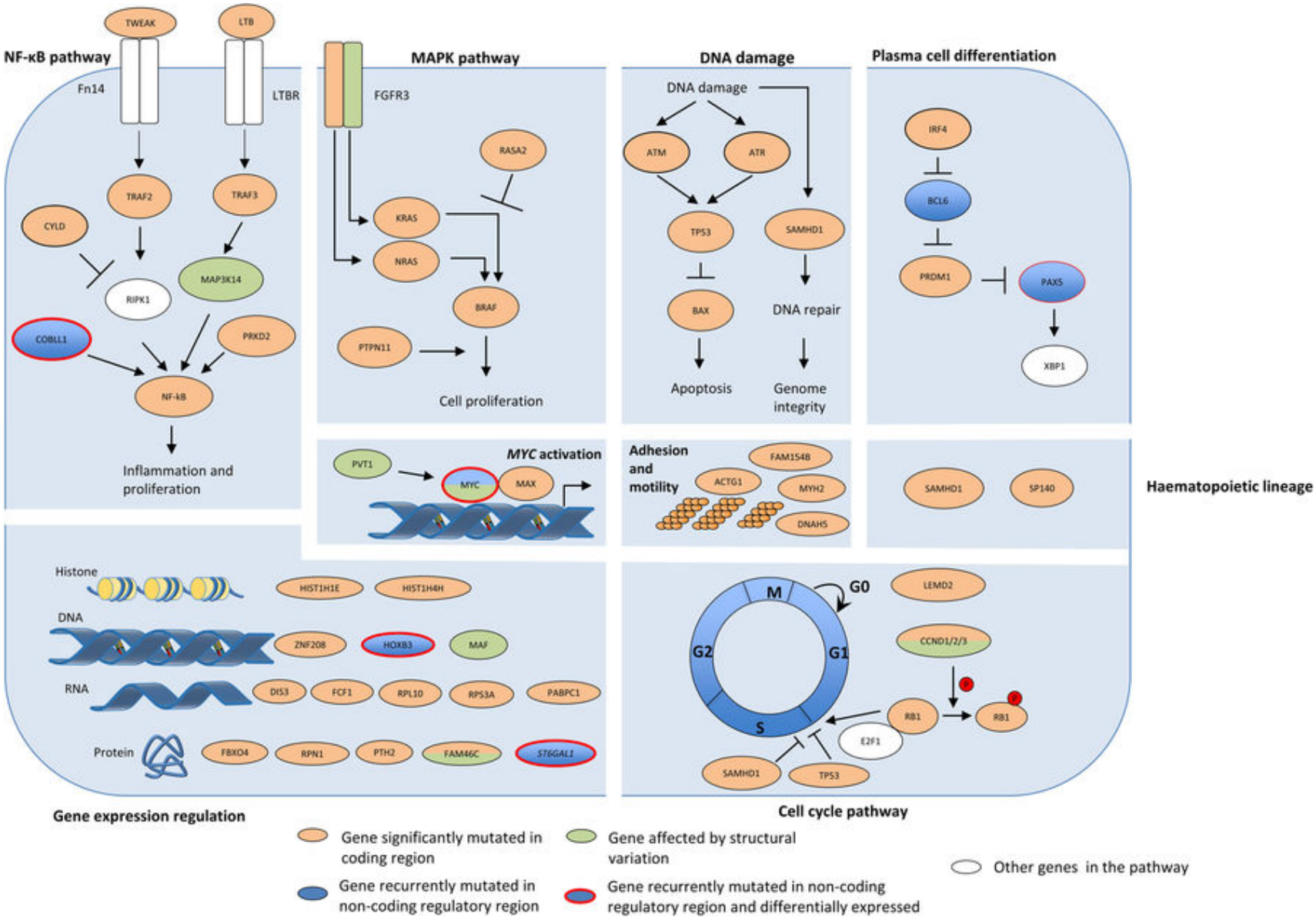
Pros:

- highly tumor specific

Cons:

- surface expression?
- myeloma cell progenitors?
- self-antigen
- pathogenic role?

Oncogenic pathways disrupted by coding and non-coding mutations in MM



Hoang PH,. Leukemia. 2018 Apr 9.

Bullet points:

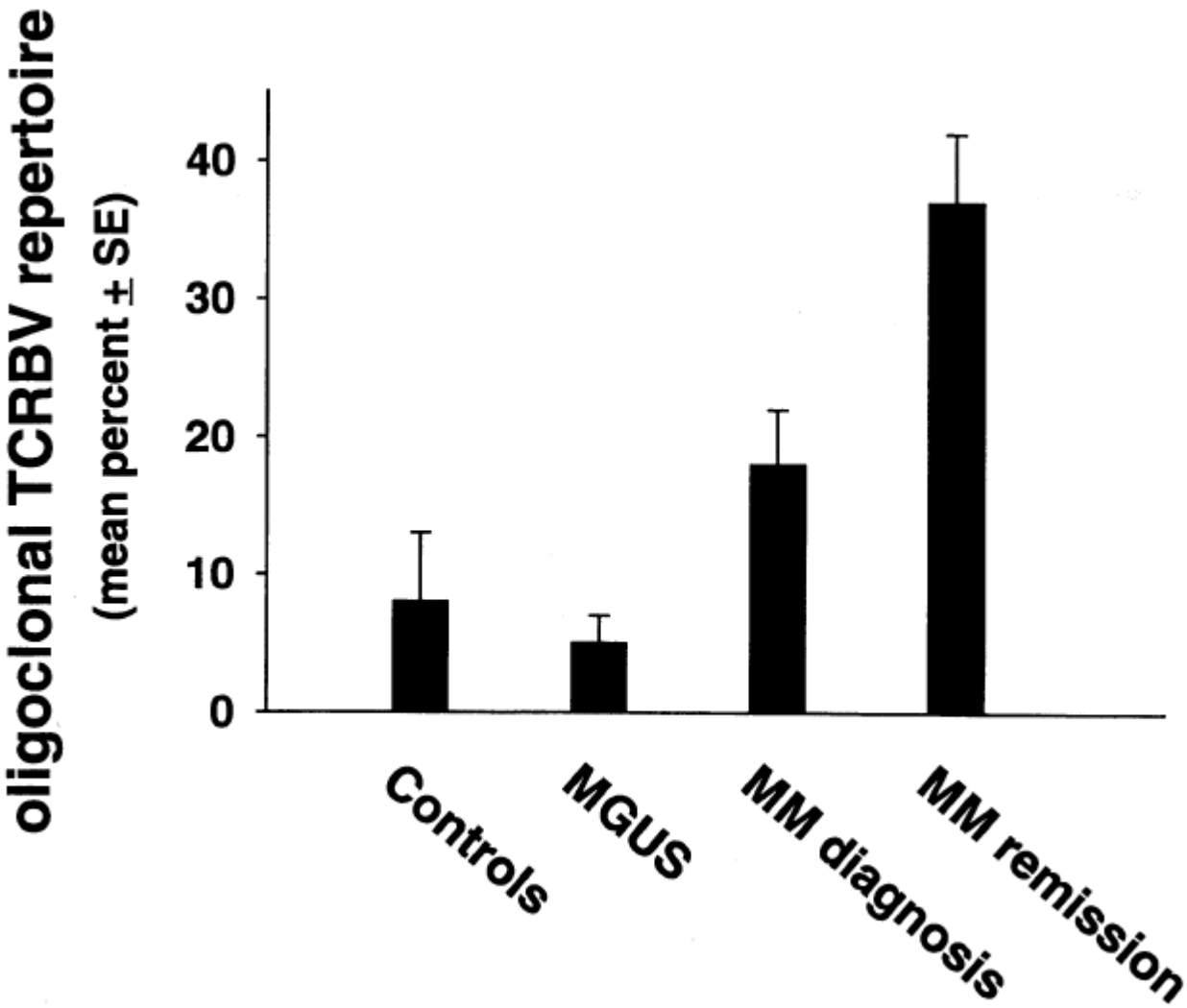
- Better TAAs than Id?

- Early & persistent immune suppressive TME commitment

- Redundancy of ICP/ICP-L pairs in TME

- Is hot or cold the TME in MM (rem vs dia etc)?

Severe and long-lasting disruption of TCR diversity after ASCT in MM

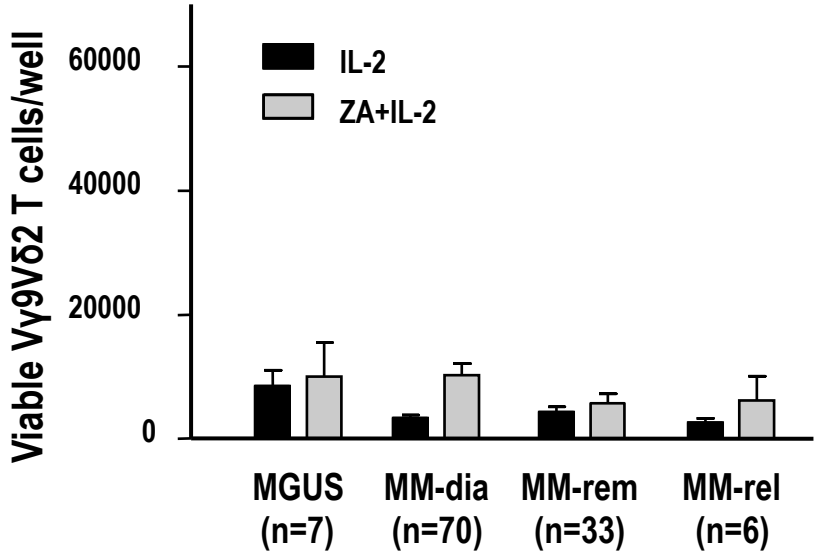


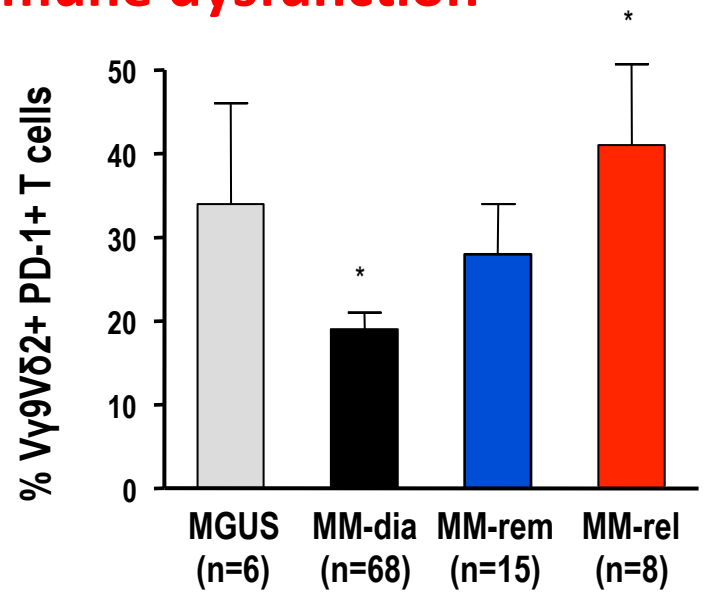
Mariani S et al., *Br J Haematol*. 113:1051-9; 2001

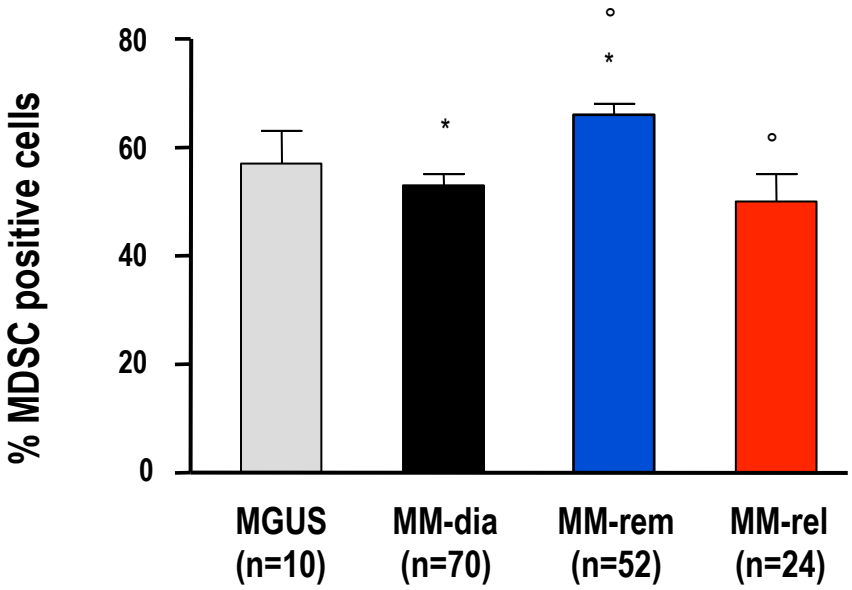
Vγ9Vδ2 T cells: early sensors of immune pollution in TME

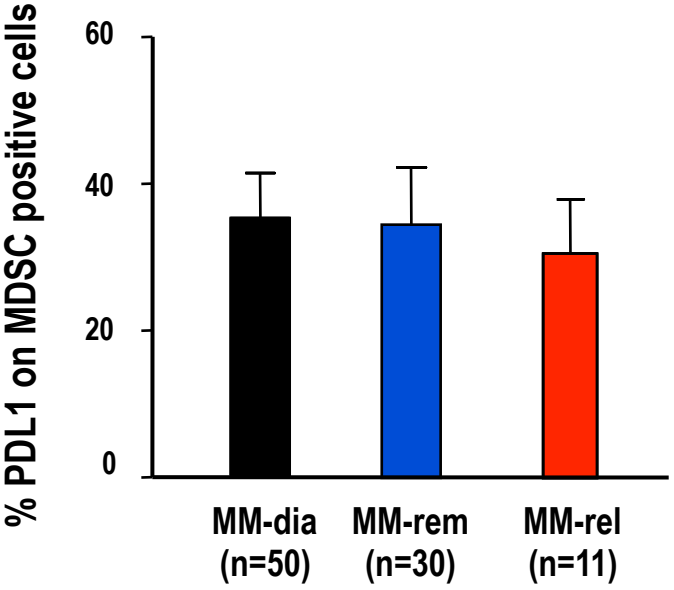
What we find depends on the tools we use
(i.e. microscope vs PCR/flow to detect MRD)

Defective ZA-reactivity of BM Vγ9Vδ2 T-cell is an early and long-lasting immune dysfunction

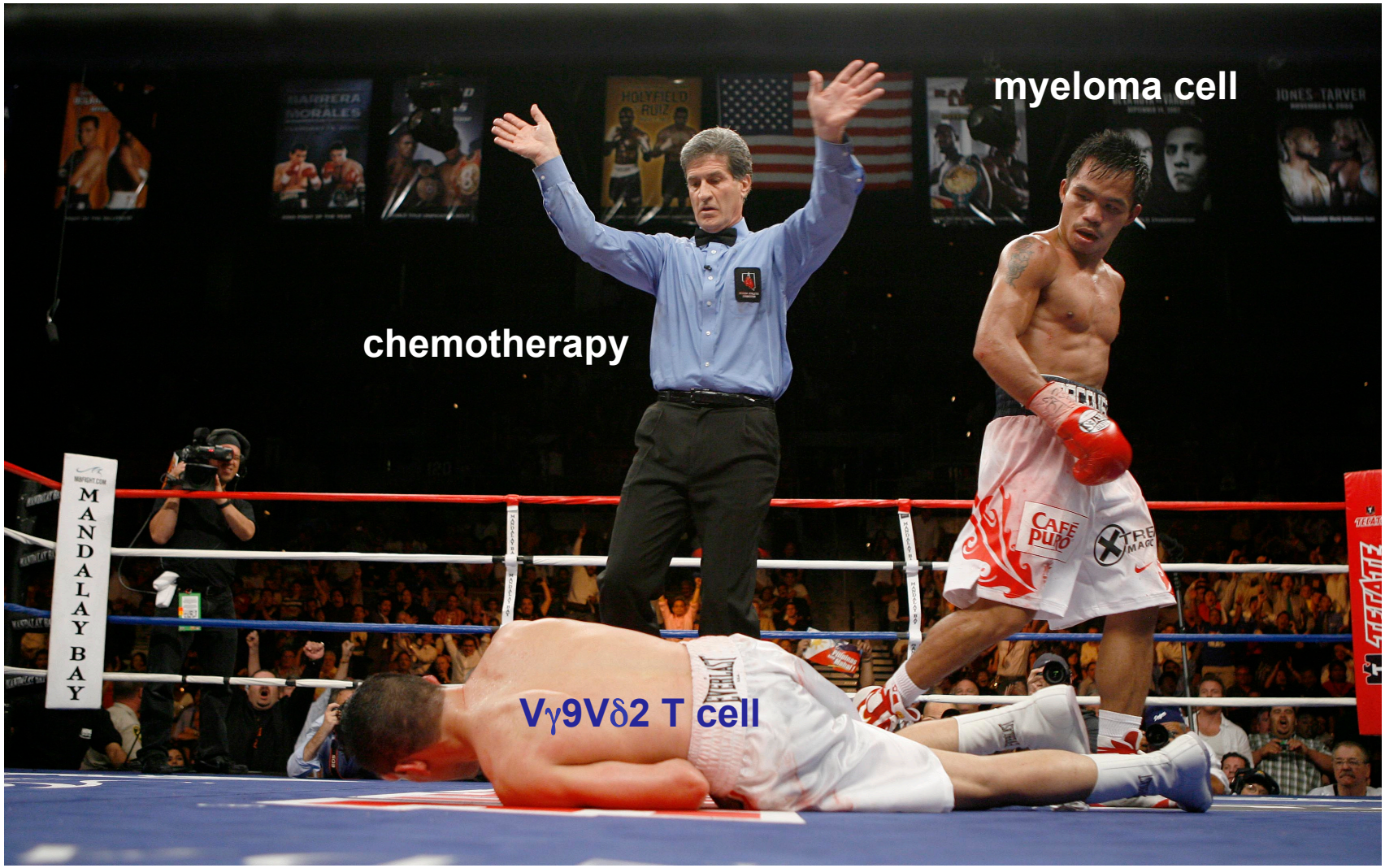








Castella, et al. *Oncoimmunology*. 2015 May 26;4(11):e1047580


myeloma cell
chemotherapy
Vγ9Vδ2 T cell
MANDALAY BAY

Bullet points:

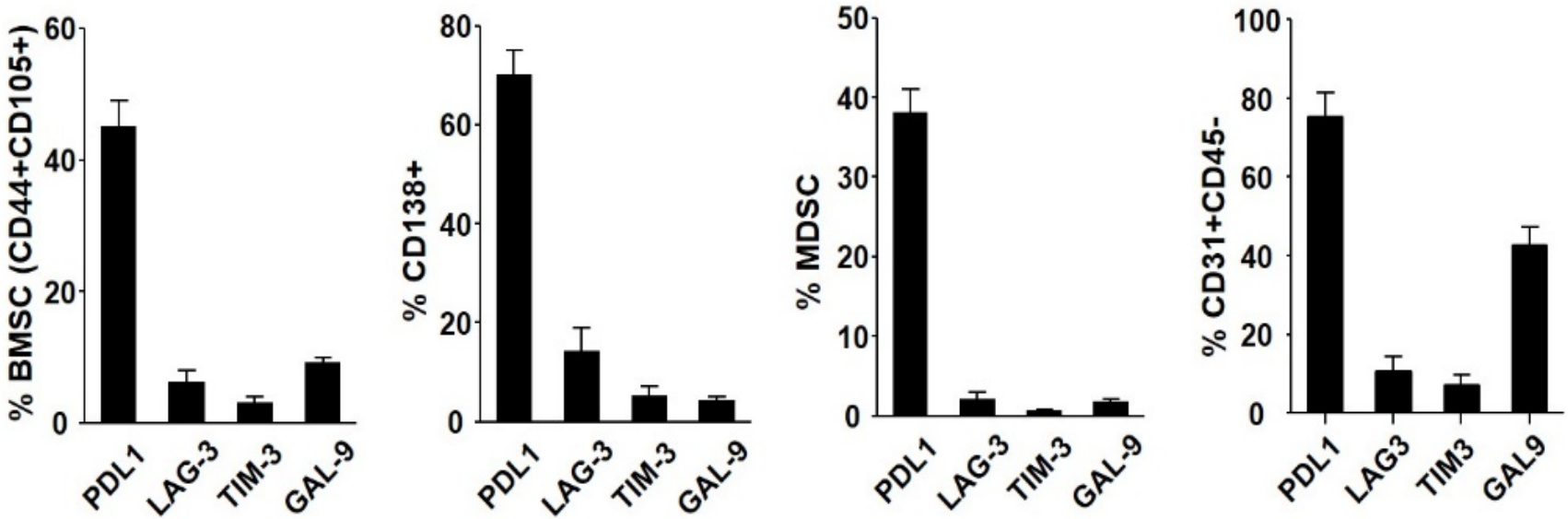
- Better TAAs than Id?

- Early & persistent immune suppressive TME commitment

- Redundancy of ICP/ICP-L pairs in TME

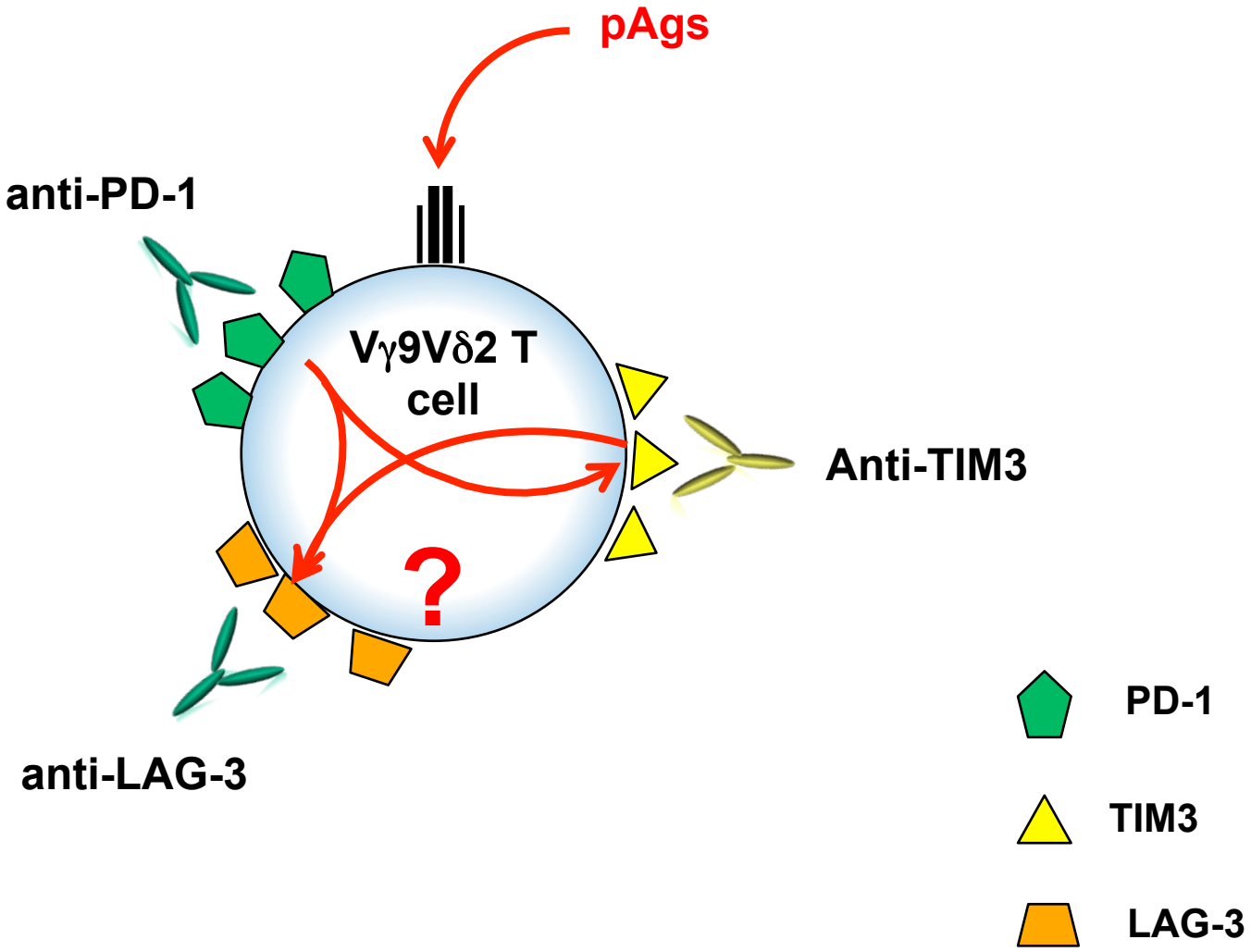
- Is hot or cold the TME in MM (rem vs dia etc)?

Immune suppressor engagers in the TME of MM patients

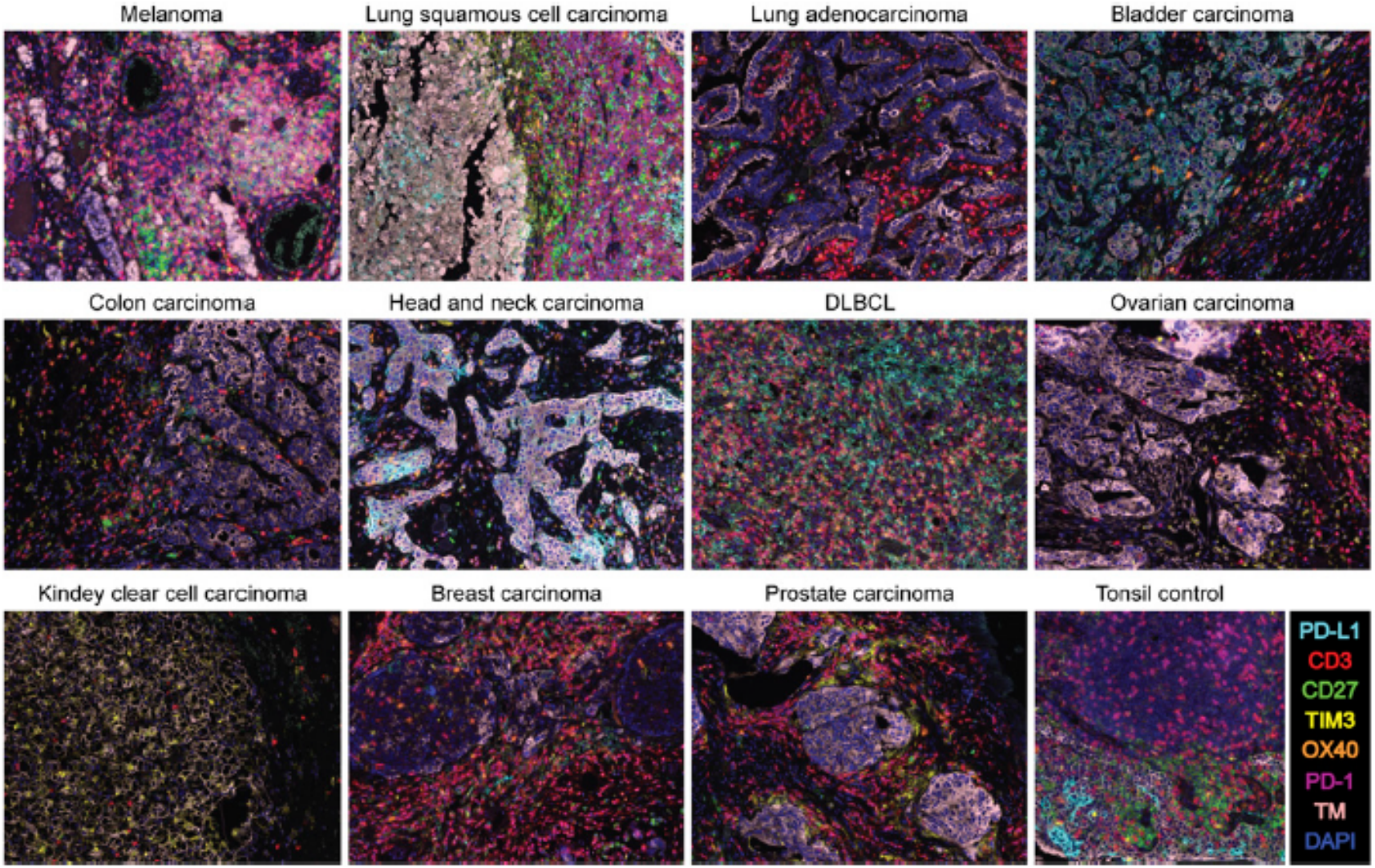


unpublished

Vγ9Vδ2 T cells as tools to dissect mechanisms of adaptive resistance to ICP inhibition



Eight-color multiplex IHC in different tumor types.



Gorris MAJ *J Immunol* published online 15 November 2017

Bullet points:

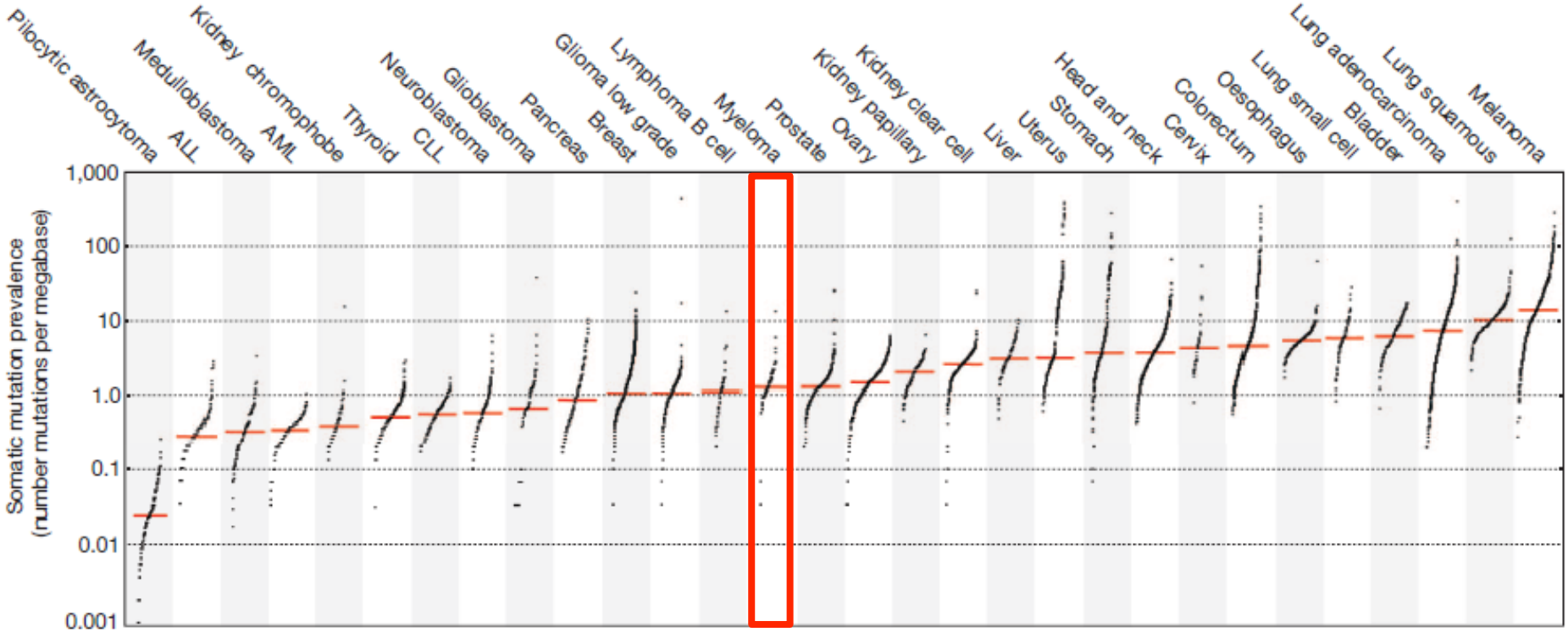
- Better TAAs than Id?

- Early & persistent immune suppressive TME commitment

- Redundancy of ICP/ICP-L pairs in TME

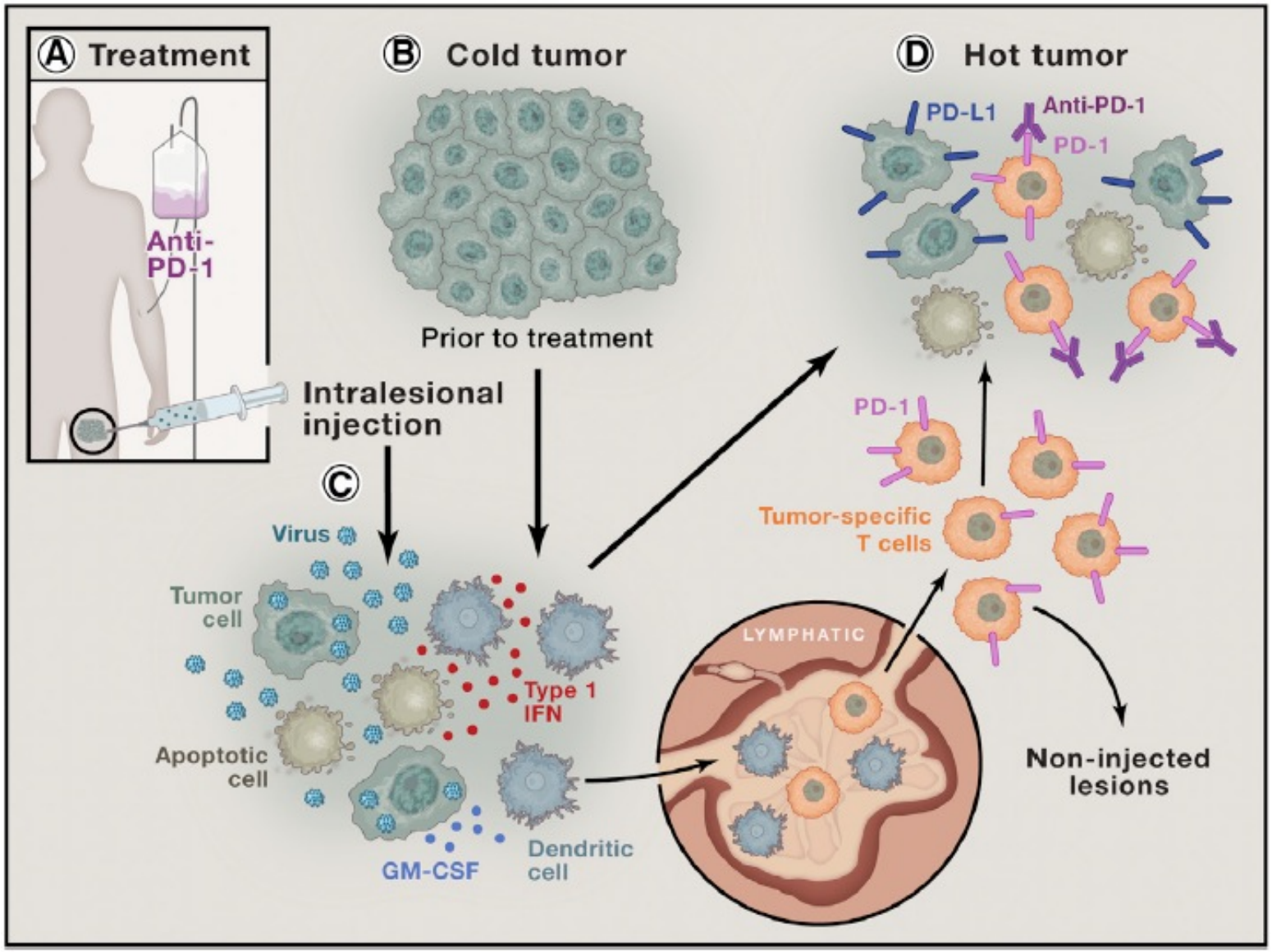
- Is hot or cold the TME in MM (rem vs dia etc)?

Mutation burden and immune responses



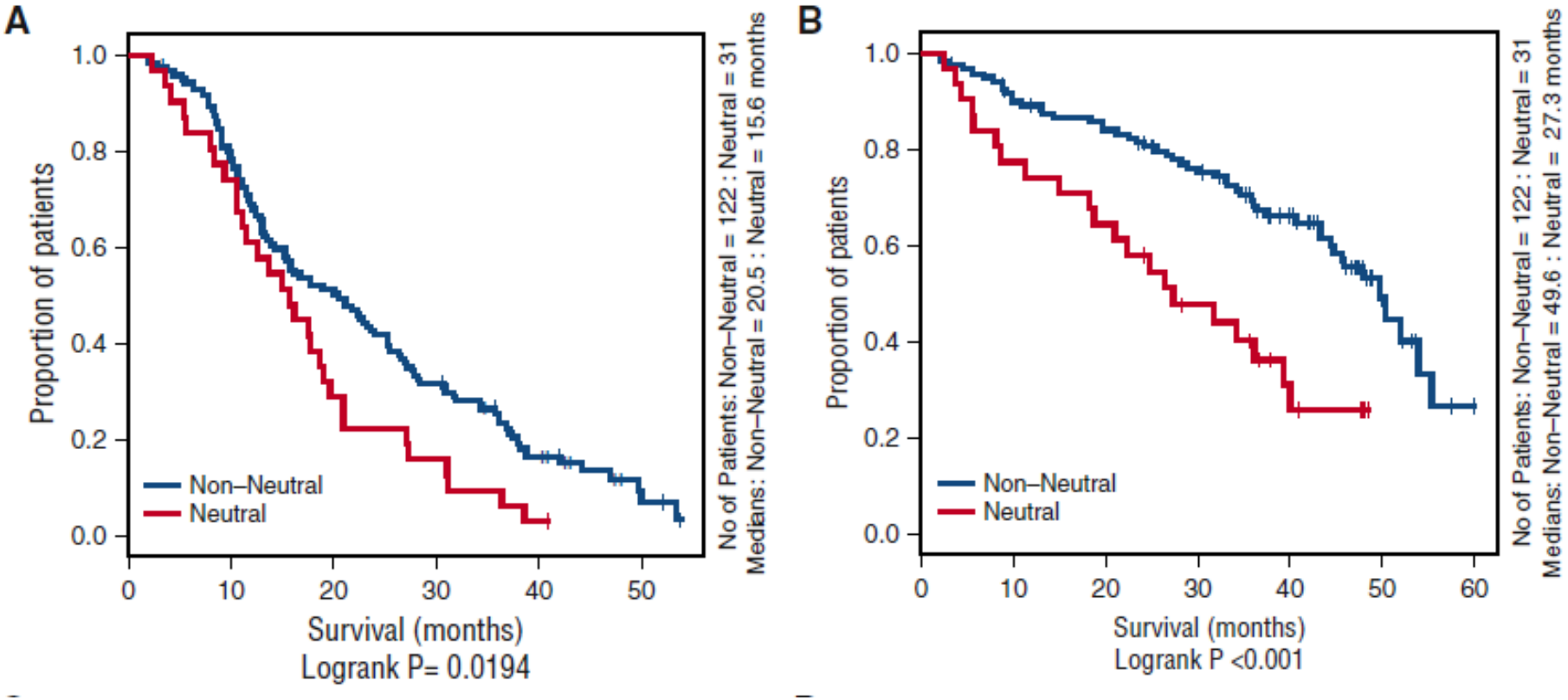
Alexandrov LB et al., *Nature*. 2013 Aug 22;500(7463):415-21.

Converting Cold into Hot Tumors



Haanen JBAG. Cell. 2017 Sep 7;170(6):1055-1056.

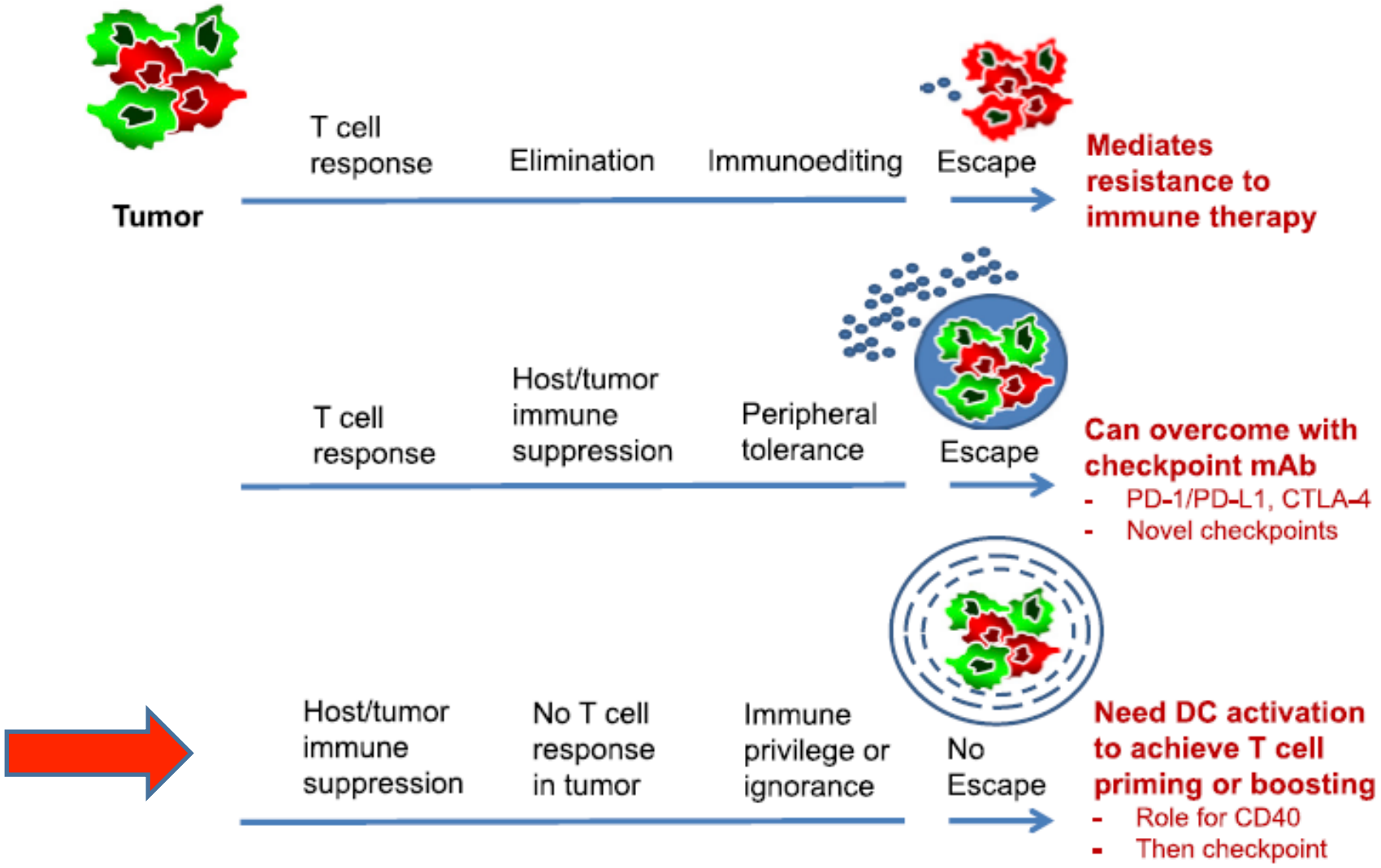
Influence of neutral evolutionary dynamics on OS and PFS in the Myeloma XI and CoMMpass studies



Neutral tumors tend to confer poorer patient survival in the context of microenvironment modulating therapies.

Johnson DC et al., *Blood*. 2017;130(14):1639-1643)

The Immune Revolution:
A Case for Priming, Not Checkpoint



Vonderheide RH.. *Cancer Cell*. 2018 Apr 9;33(4):563-569

Credits

Laboratory of Blood Tumor Immunology, CeRMS

Barbara Castella (Senior Lab Investigator)

Ezio Tripoli

Claudia Gianotta

Division of Hematology, Cuneo, Italy

Mariella Grasso

Margherita Bonferrroni

Claudia Castellino

Myriam Foglietta

Daniele Mattei

Nicola Mordini

Davide Rapezzi

Roberto Sorasio

University of Bari, Italy

Angelo Vacca

Roberto Ria

Assunta Melaccio

Department of Oncology, Turin, Italy

Chiara Riganti

Joanna Kopecka

Division of Hematology, Turin, Italy

Mario Boccadoro

Francesca Gay

Alessandra Larocca

Sara Bringhen

Division of Hematology - FACS lab

Paola Omedè

Vittorio Muccio

Milena Gilestro

Marina Ruggeri

Lab of Immunogenetics, Turin

Fabio Malavasi

Ada Funaro

AACR American Association for Cancer Research

International Myeloma Foundation

AIRC

Ministero Istruzione Università e Ricerca

REGIONE PIEMONTE