SITC 2017

November 8-12

NATIONAL HARBOR
MARYLAND

Gaylord National Hotel
& Convention Center

sitc

Society for Immunotherapy of Cancer

Acquired Resistance in Melanoma

- following its genetic evolution -

Annette Paschen

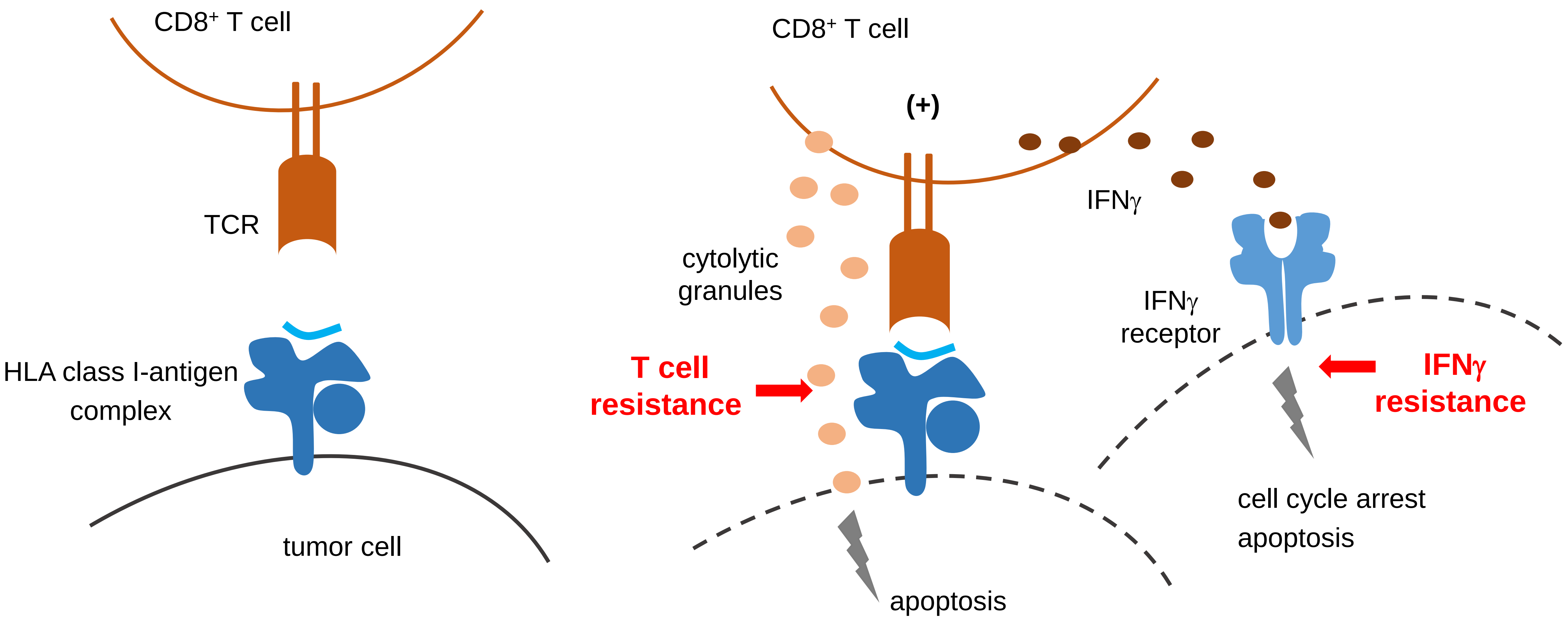
sitc
Society for Immunotherapy of Cancer

Presenter Disclosure Information

Annette Paschen

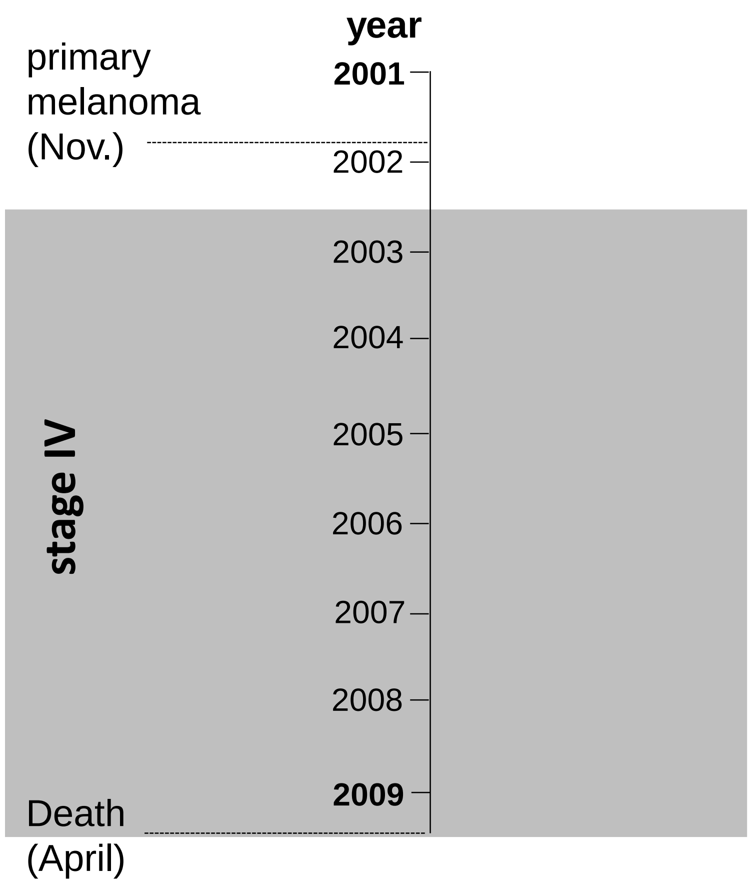
No Relationships to Disclose

Tumor Cell Killing by Cytotoxic CD8$^+$ T Cells



Clinical History of Patient Ma-Mel-86

Patient Ma-Mel-86



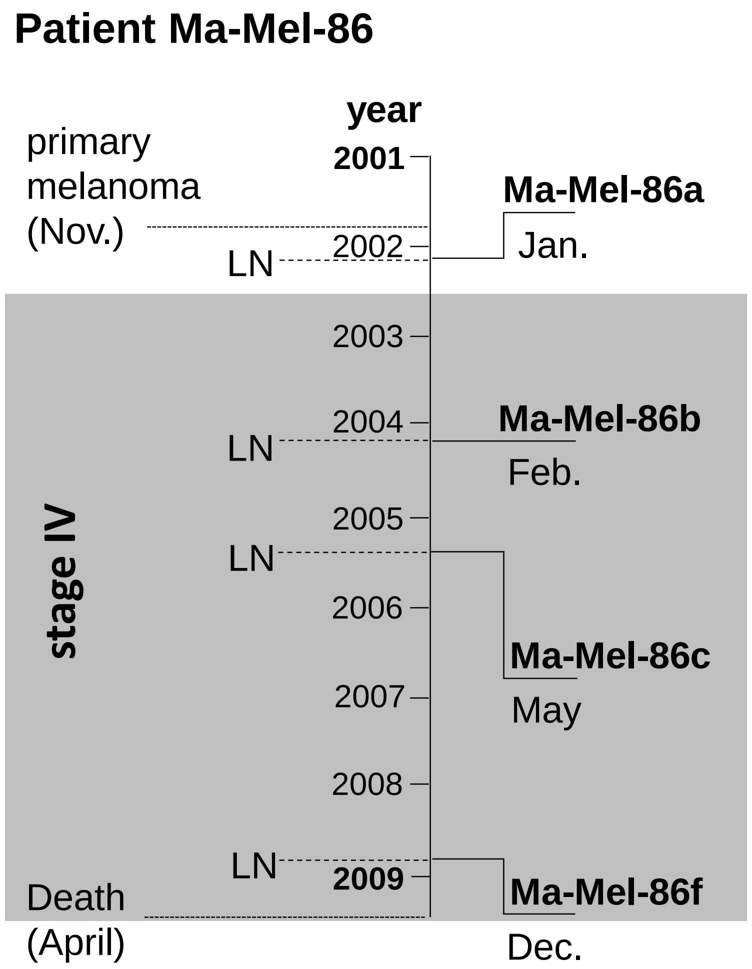
2001, November:	primary melanoma diagnosed
2002, January:	stage III
2002, September:	stage IV
2002/2003:	multiple brain metastases, regression upon irradiation
2005:	colon metastases
2005-2008:	<u>clinically disease-free interval</u>
2009:	recurrent metastases, death

Long-term survivor !

Immunotherapy: IFNα, peptide-based vaccine,
tumor lysate-loaded DC vaccine

Zhao et al., Cancer Res 2016

Clinical History of Patient Ma-Mel-86



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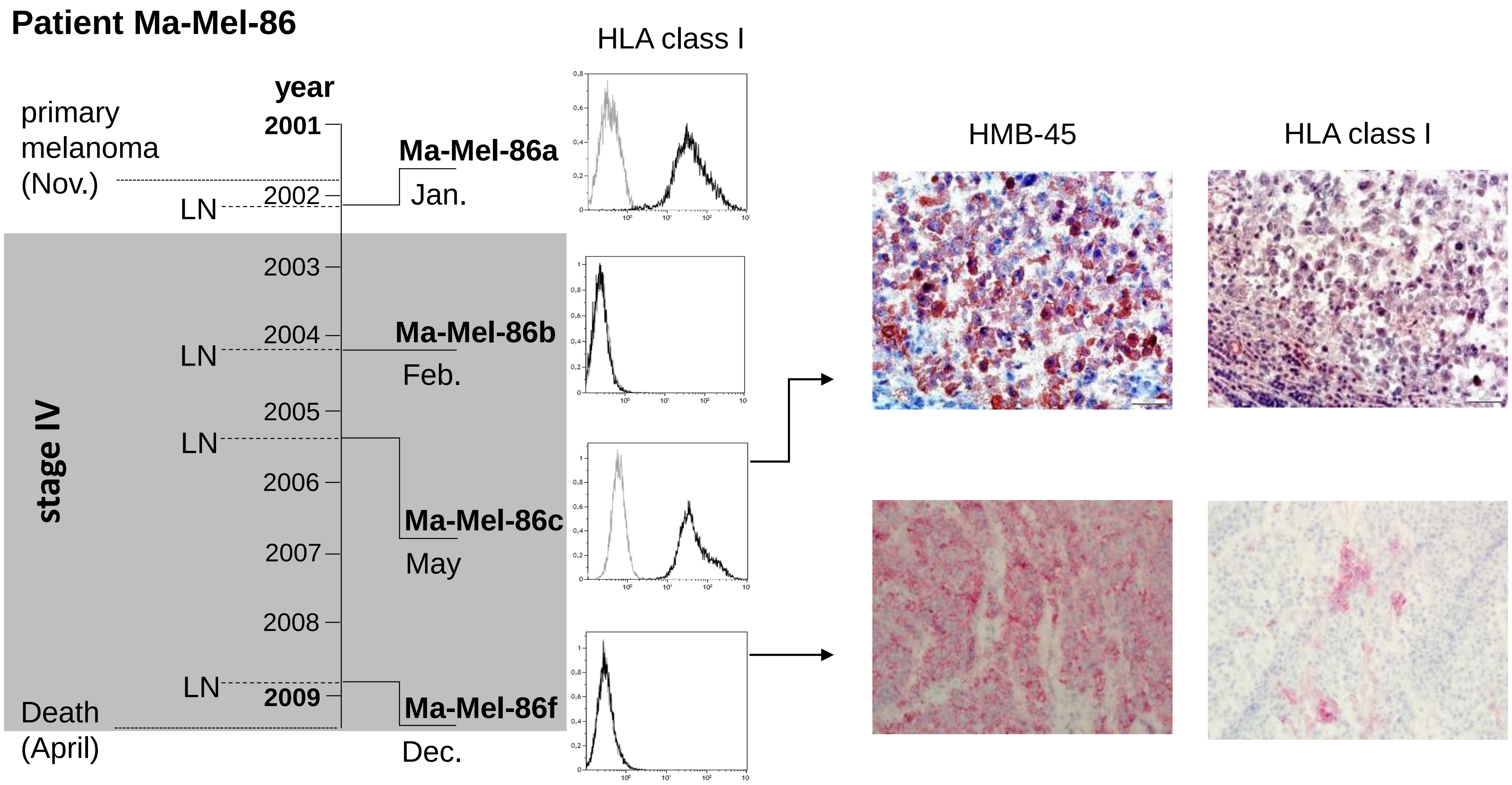
Zhao et al., Cancer Res 2016

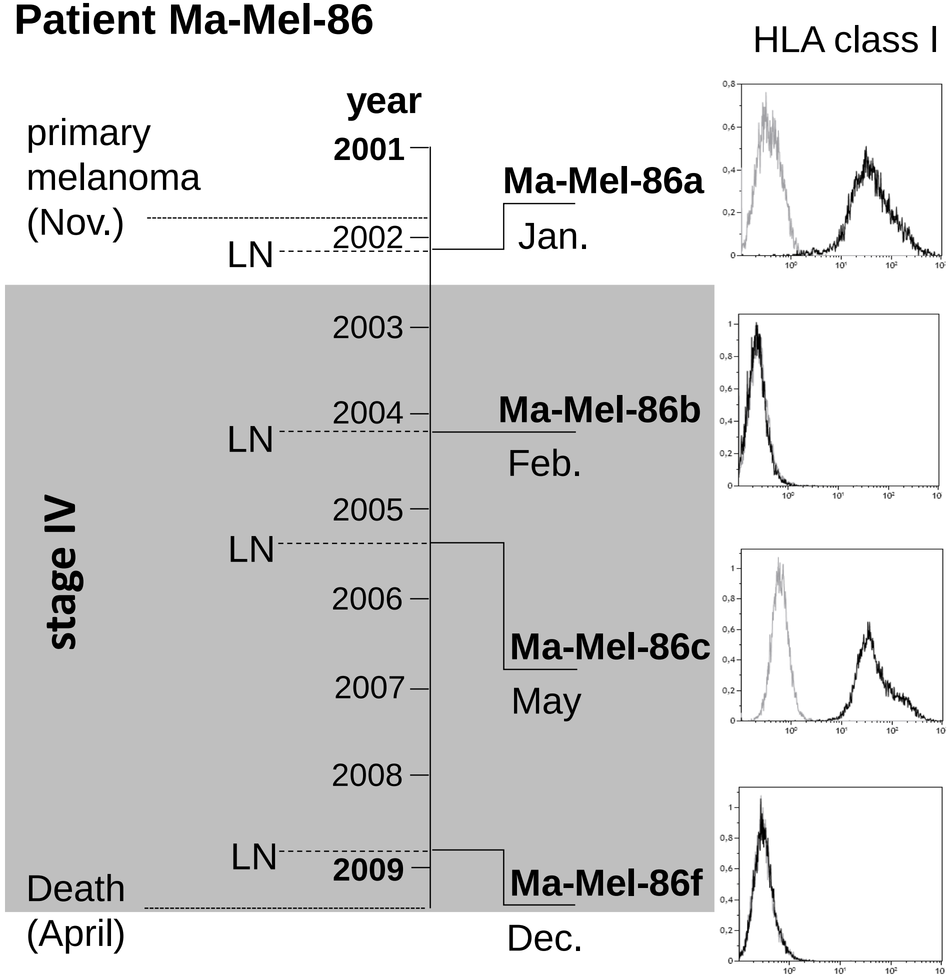
Heterogenous HLA Class I expression



Zhao et al., Cancer Res 2016

Detection of Neoantigen-specific CD8⁺ T cells (Tc)

Patient Ma-Mel-86



neoantigen	HLA restriction	Expression
PRDM10 ^{S1050F}	HLA-A*24:02	86a
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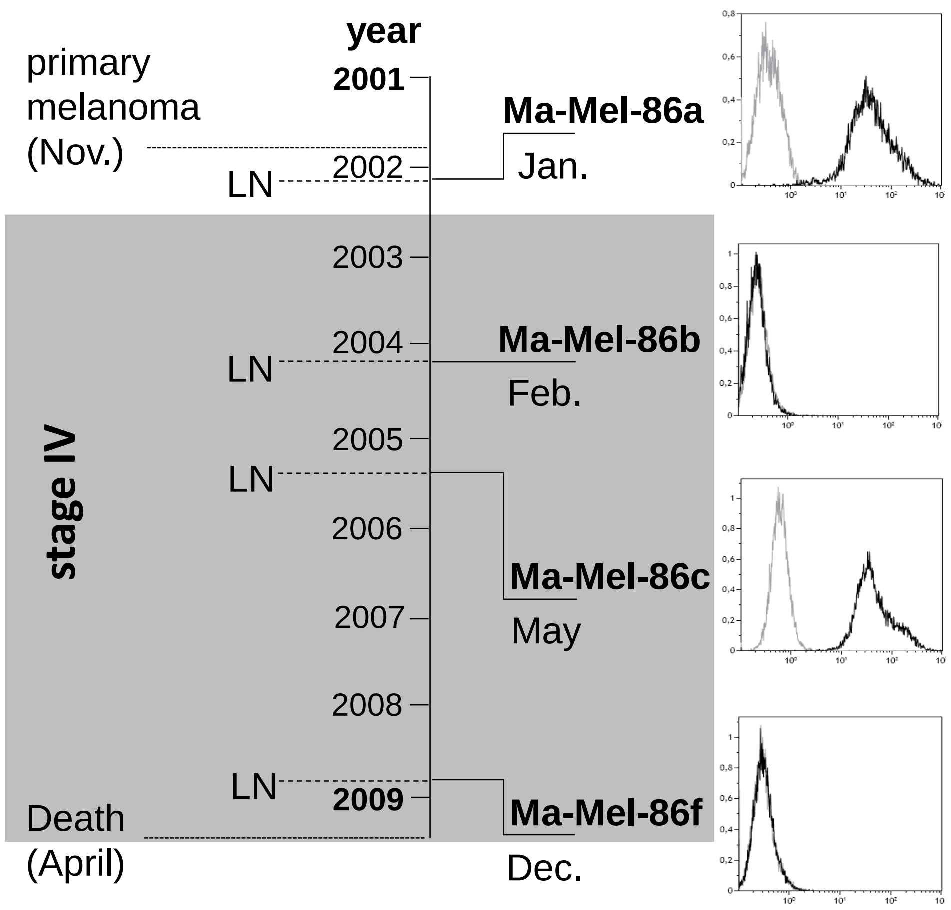
Thomas Wölfel (University Mainz, Germany)

Schrörs et al., Oncotarget 2017
Zhao et al., Cancer Res 2016

Detection of Neoantigen-specific CD8+ T cells (Tc)

Patient Ma-Mel-86



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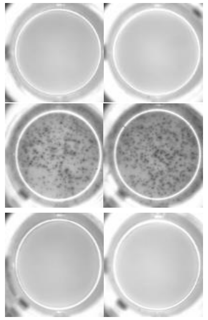
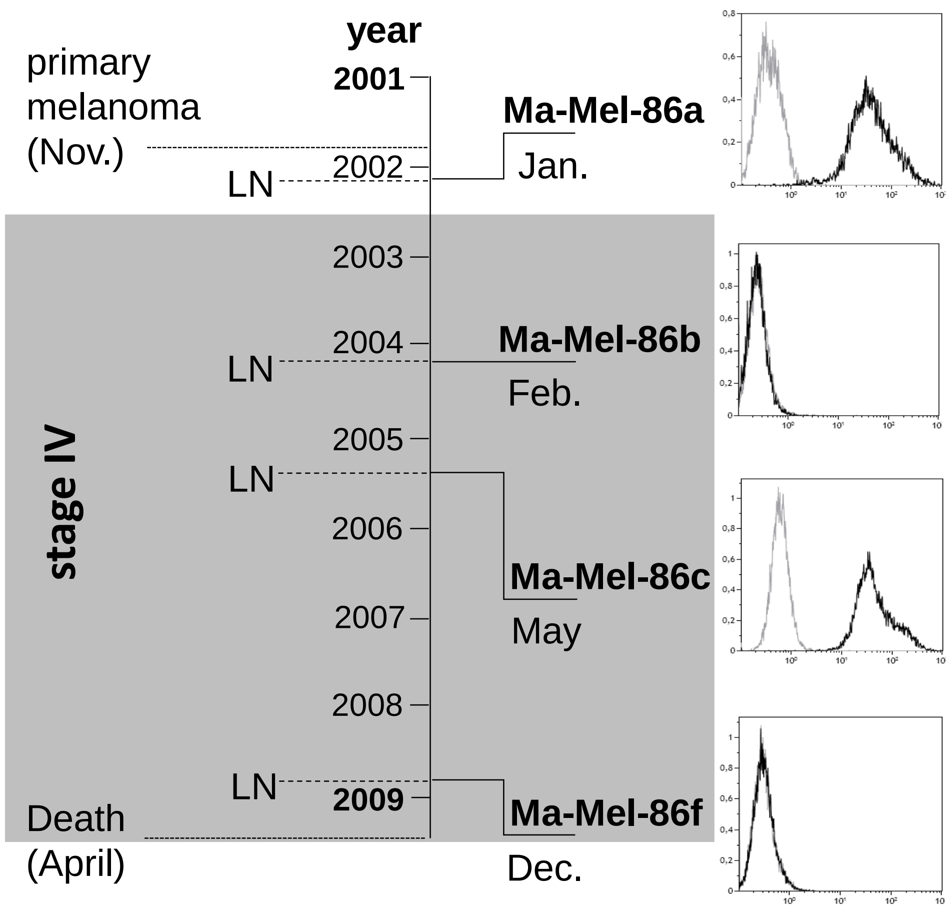
HERPUD1^{G161S}-specific Tc



Schrörs et al., Oncotarget 2017
Zhao et al., Cancer Res 2016

Detection of Neoantigen-specific CD8$^+$ T cells (Tc)

Patient Ma-Mel-86



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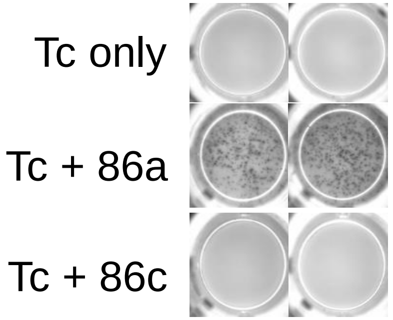
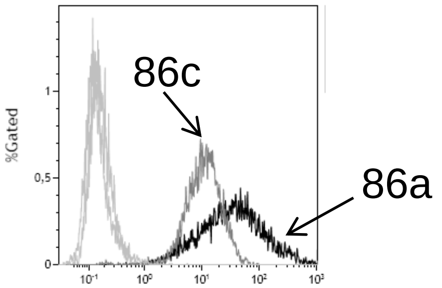
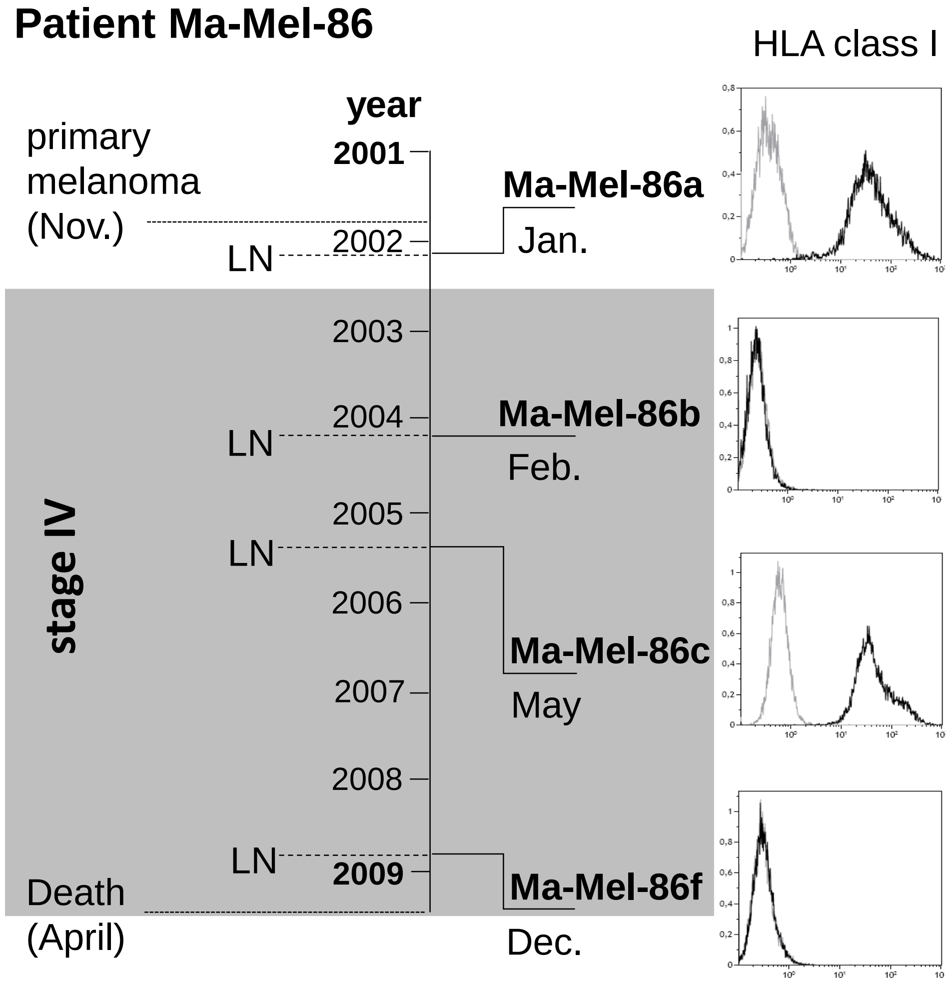


HLA class I



Schrörs et al., Oncotarget 2017
Zhao et al., Cancer Res 2016

HLA Haplotype Loss Protects from Neoantigen-specific Tc



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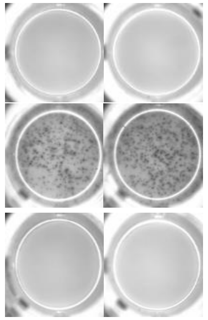
HERPUD1^{G161S}-specific Tc

Tc only

Tc + 86a

Tc + 86c



Ma-Mel-86a

HLA-A	*01:01 / *24:02
HLA-B	*08:01 / *15:01
HLA–Cw	*07:01 / *03:03

Ma-Mel-86c

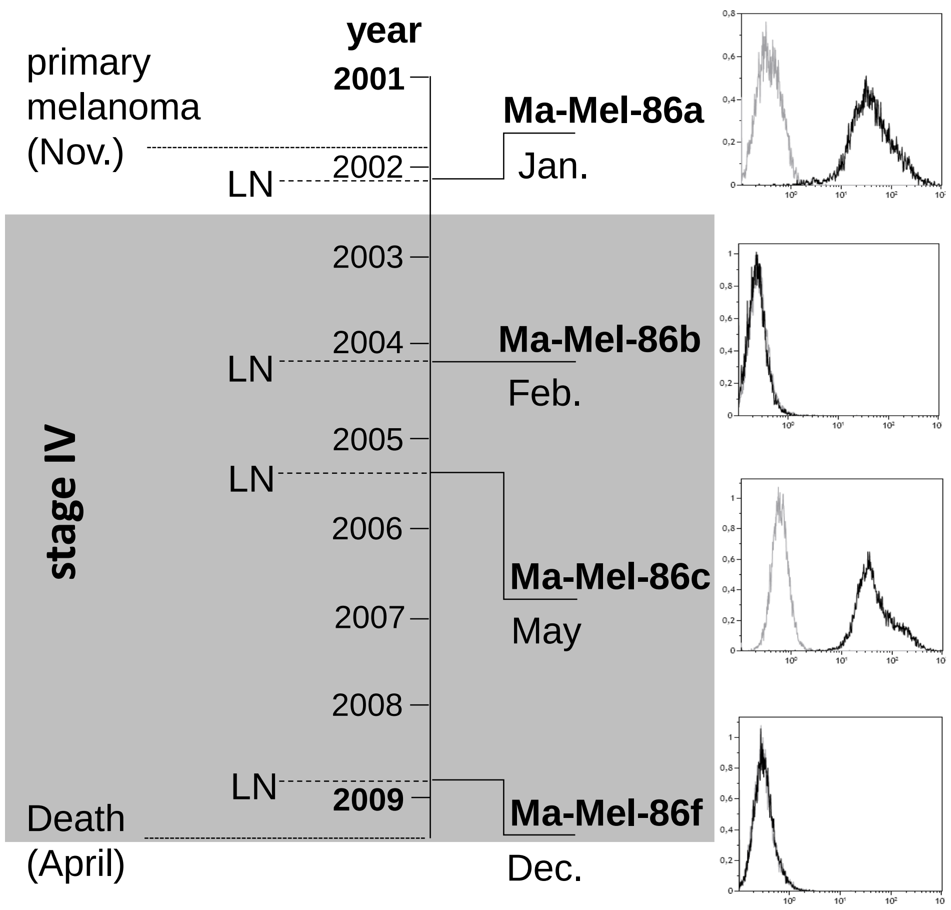
HLA-A	*01:01 / -
HLA-B	*08:01 / -
HLA–Cw	*07:01 / -

Schrörs et al., Oncotarget 2017
Zhao et al., Cancer Res 2016

HLA Haplotype Loss Protects from Neoantigen-specific Tc

Patient Ma-Mel-86

HLA class I



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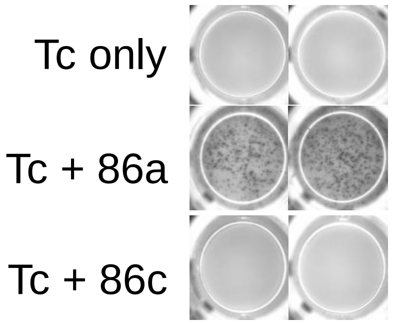
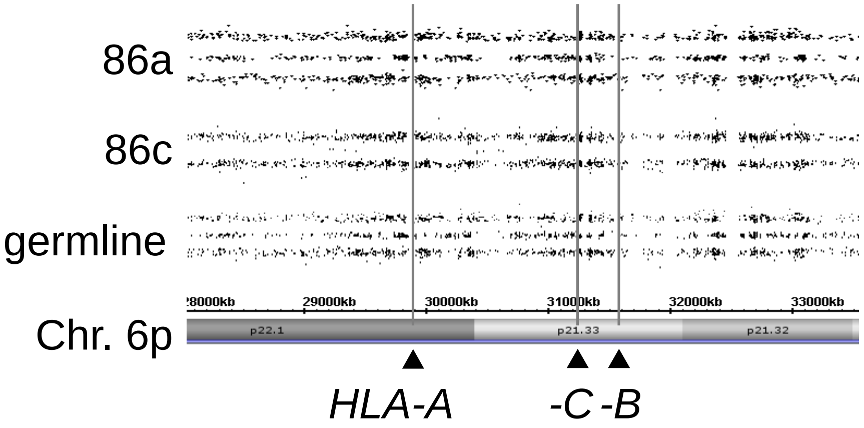
HERPUD1^{G161S}-specific Tc



Allelic distribution



Schrörs et al., Oncotarget 2017
Zhao et al., Cancer Res 2016

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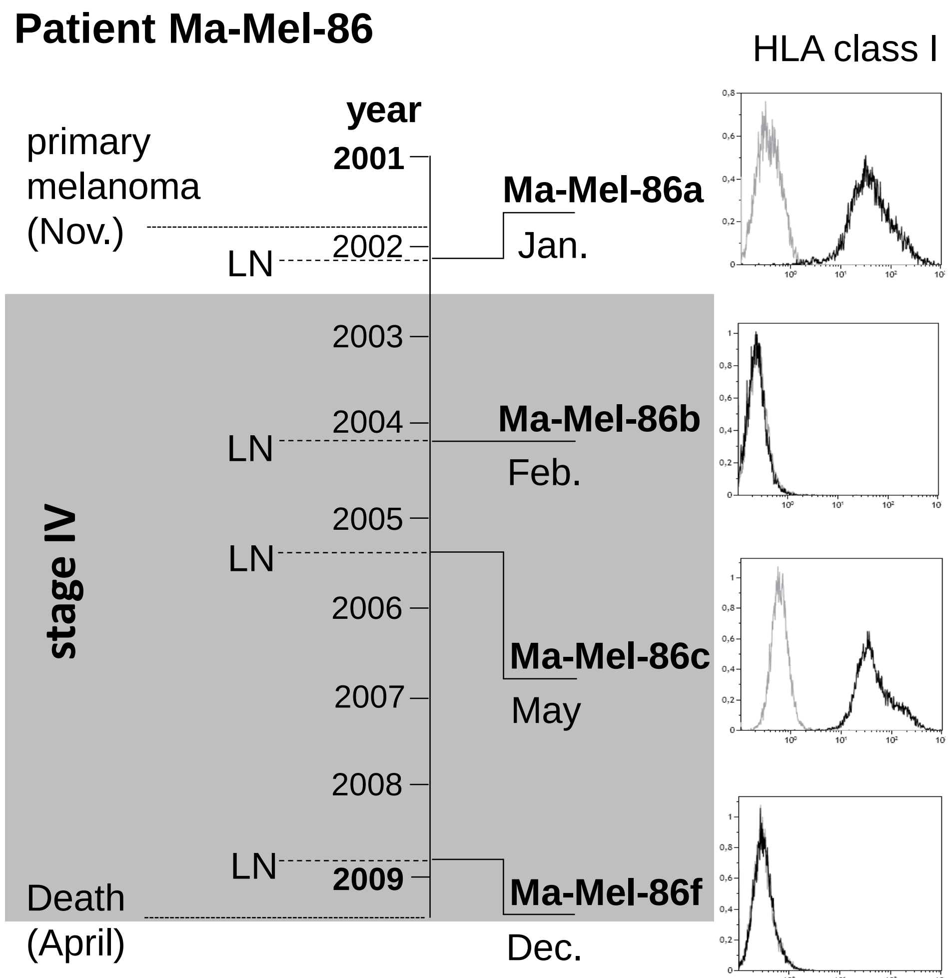

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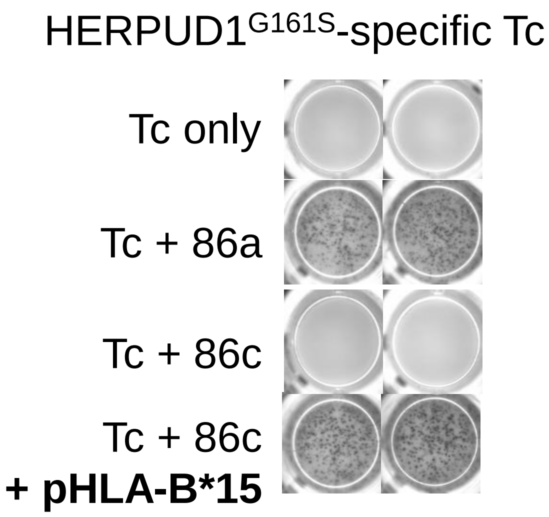
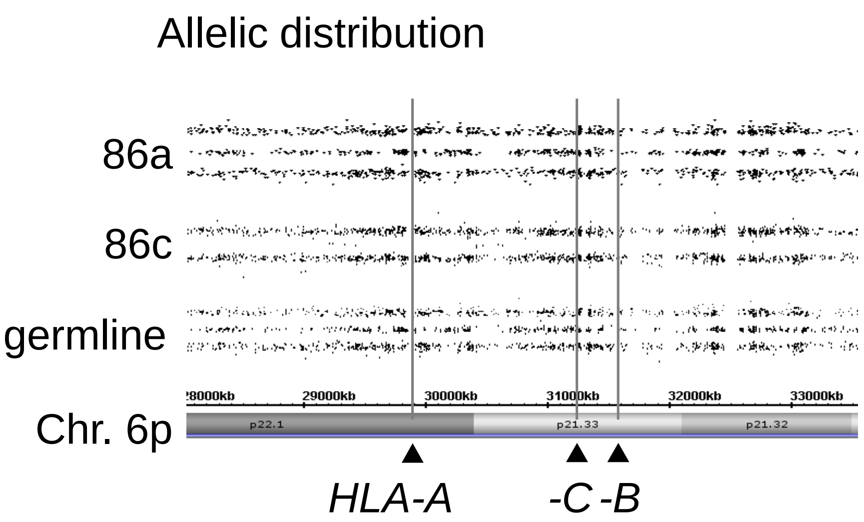
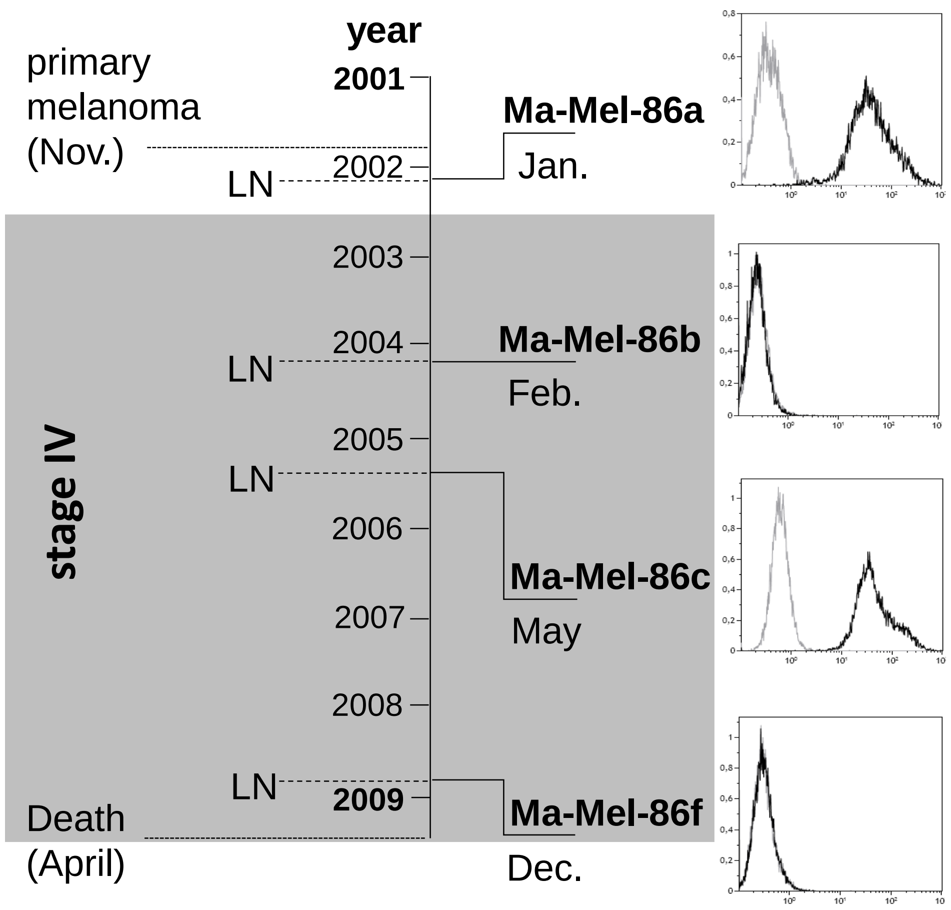


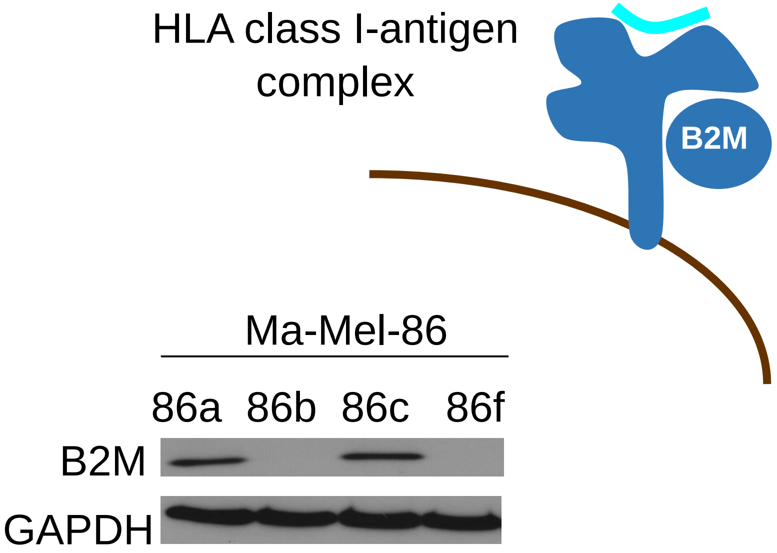


Schrörs et al., Oncotarget 2017
Zhao et al., Cancer Res 2016

T Cell Resistance by Acquired B2M Deficiency

Patient Ma-Mel-86





Zhao et al., Cancer Res 2016

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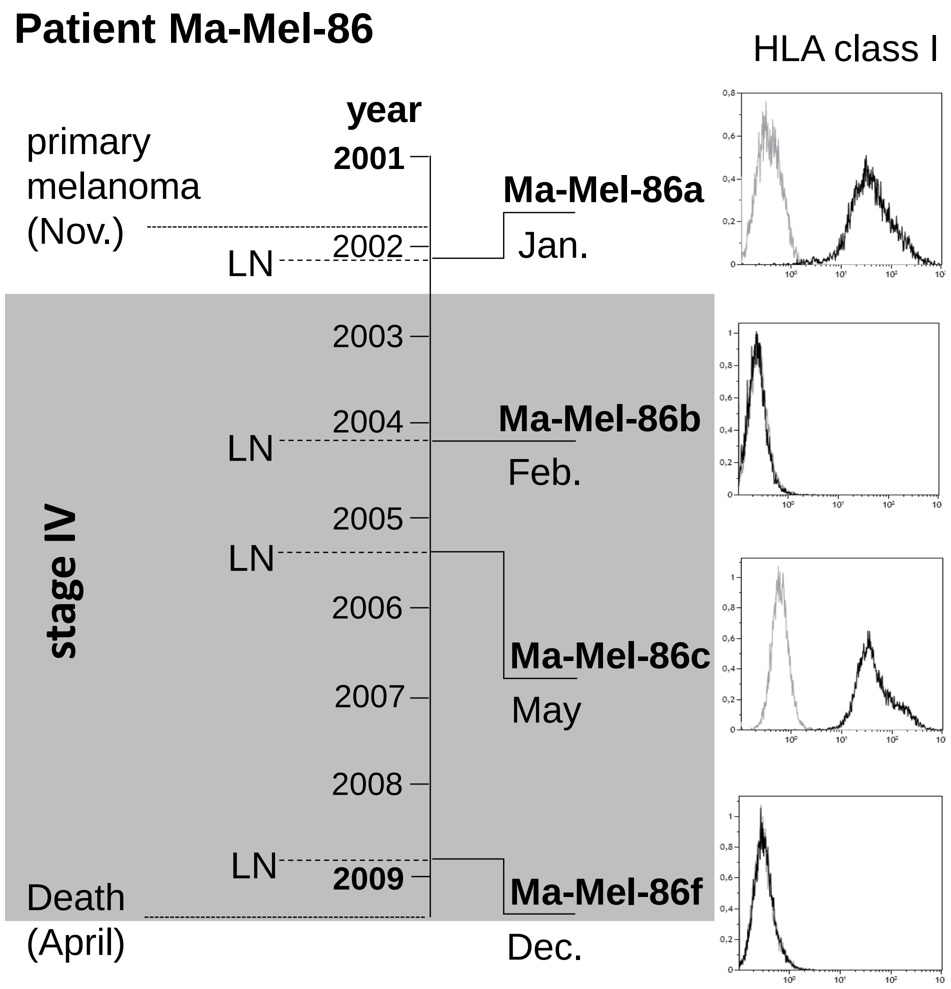

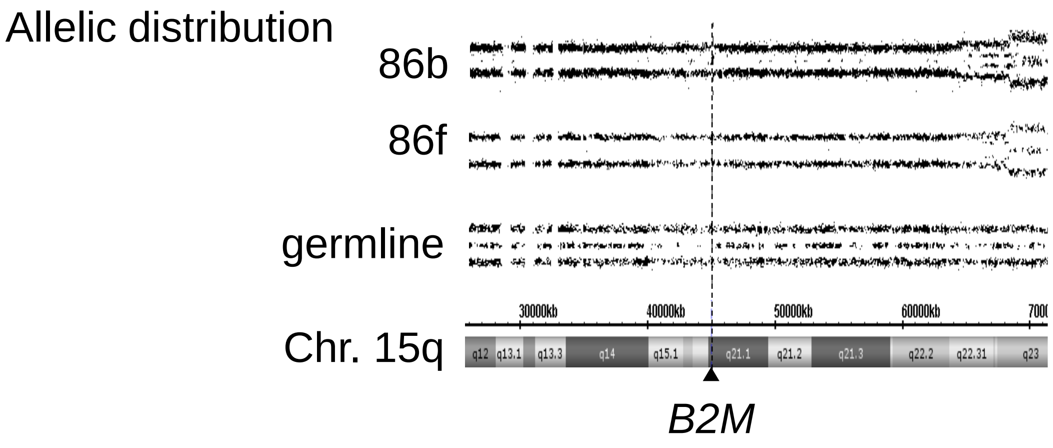

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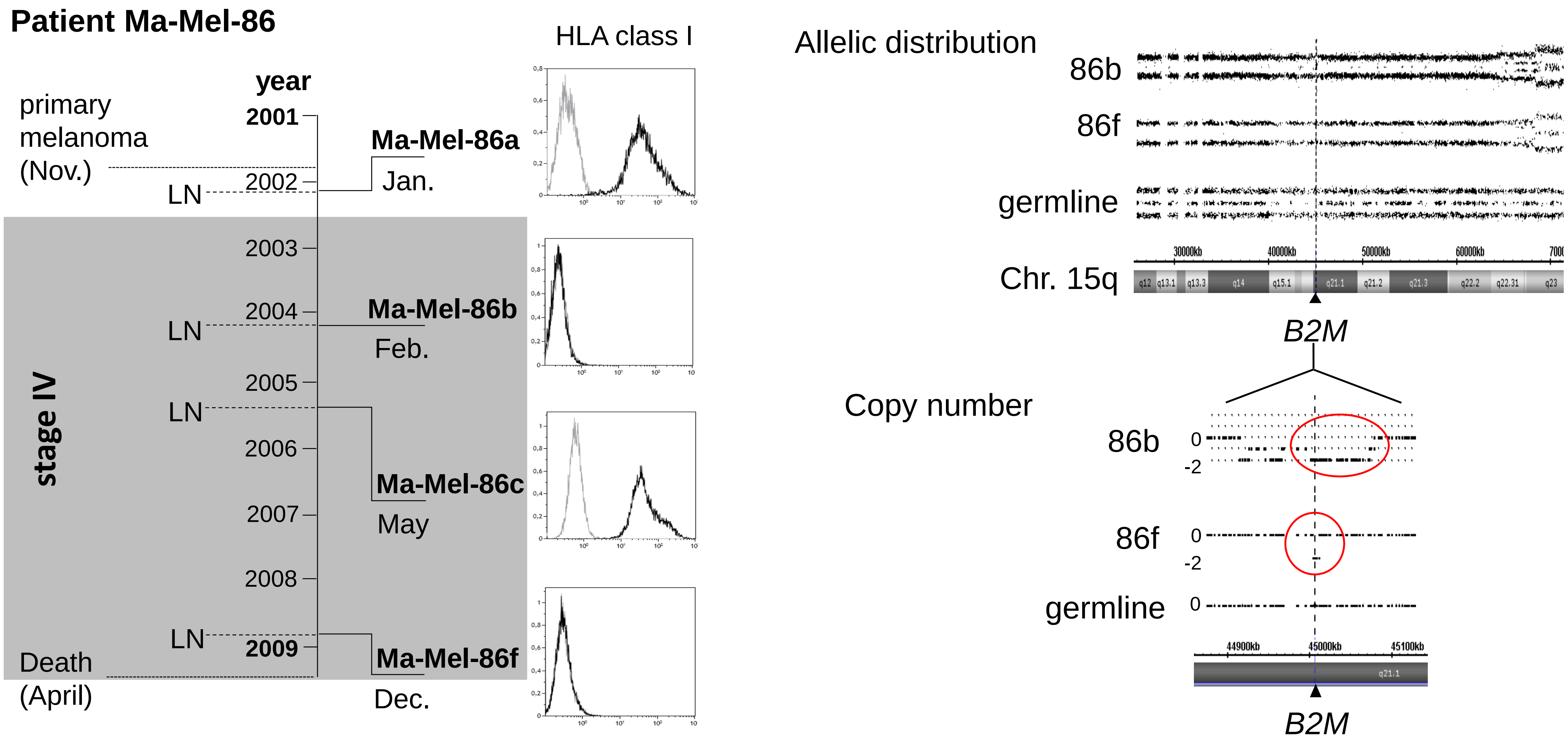
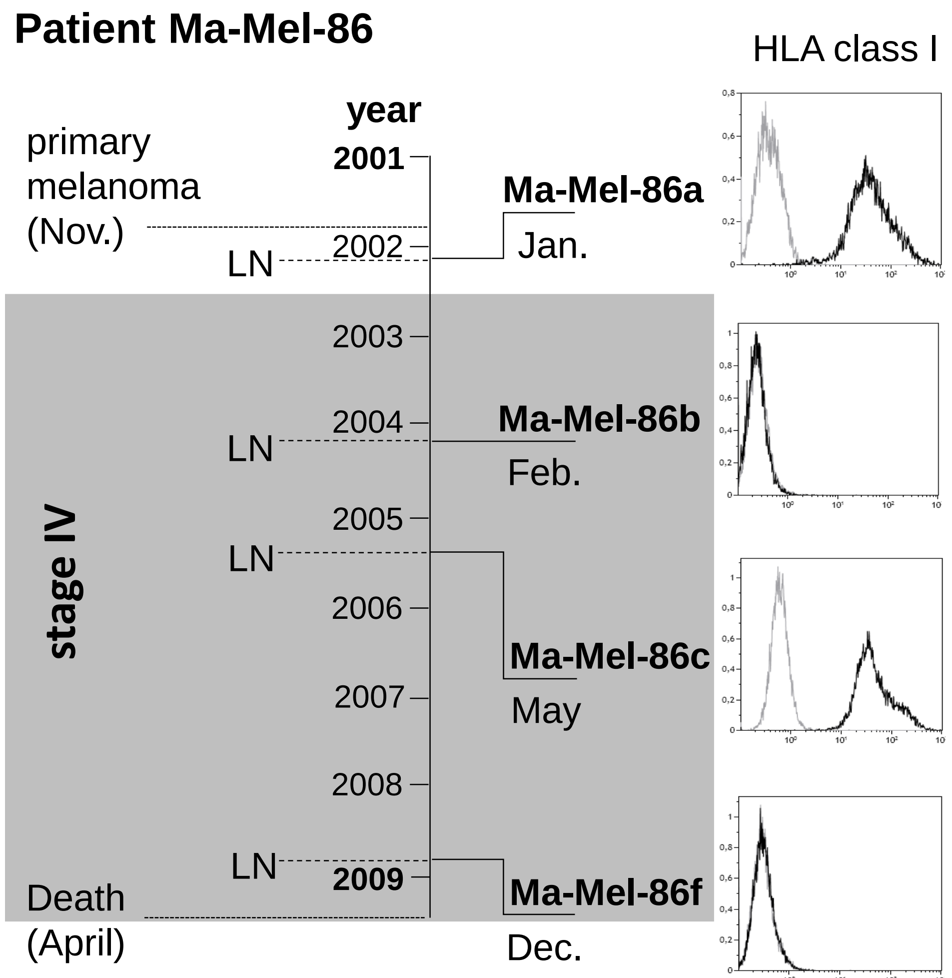
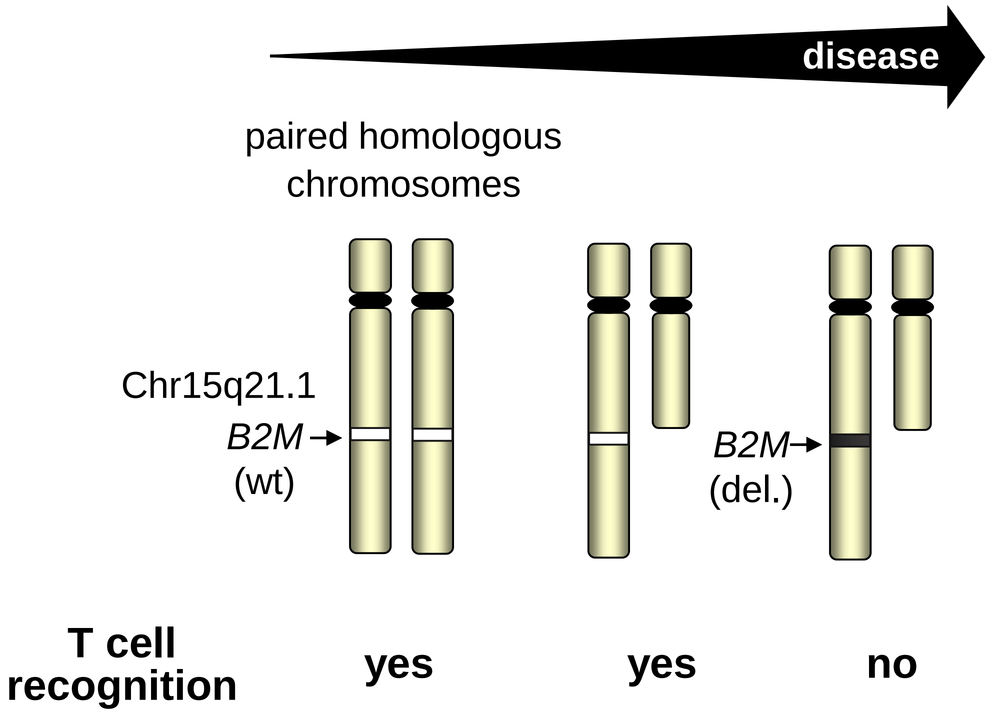


Zhao et al., Cancer Res 2016

Evolution of T Cell Resistance



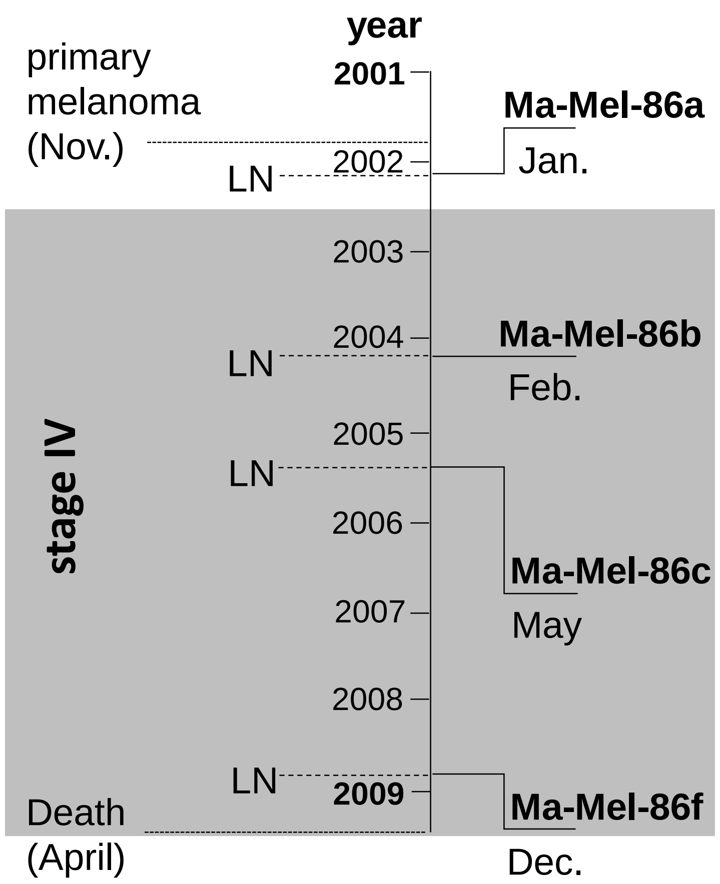


Similar evolution in two additional patient models
(Sucker et al., Clin Cancer Res. 2014)

Zhao et al., Cancer Res 2016

Multiple Acquired Resistance Mechanisms in Ma-Mel-86

Patient Ma-Mel-86



- Resistance to neoantigen-specific T cells by HLA haplotype loss due to chromosome 6p aberrations
- T cell resistance due to acquired B2M deficiency caused by shared chromosome 15q aberrations and independent *B2M* gene deletions

Multiple Acquired Resistance Mechanisms in Ma-Mel-86

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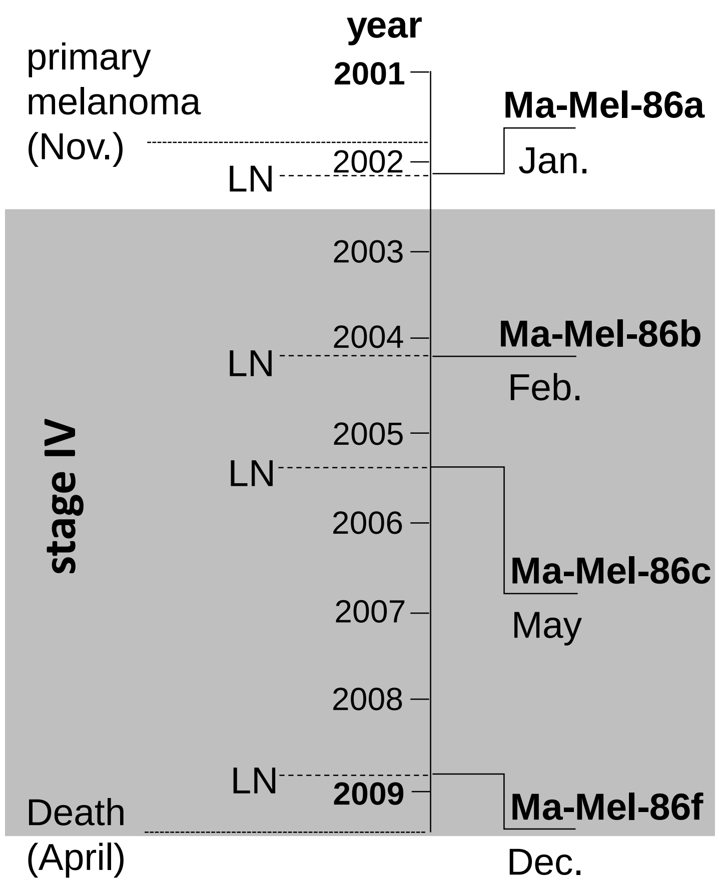

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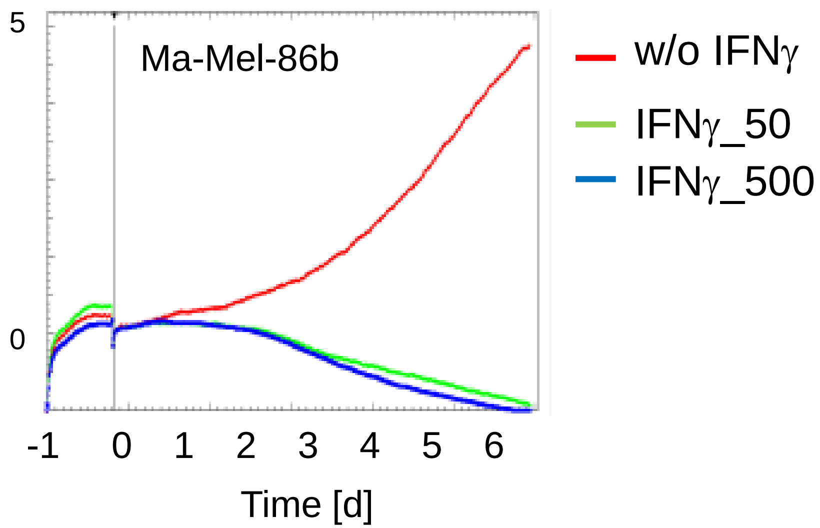
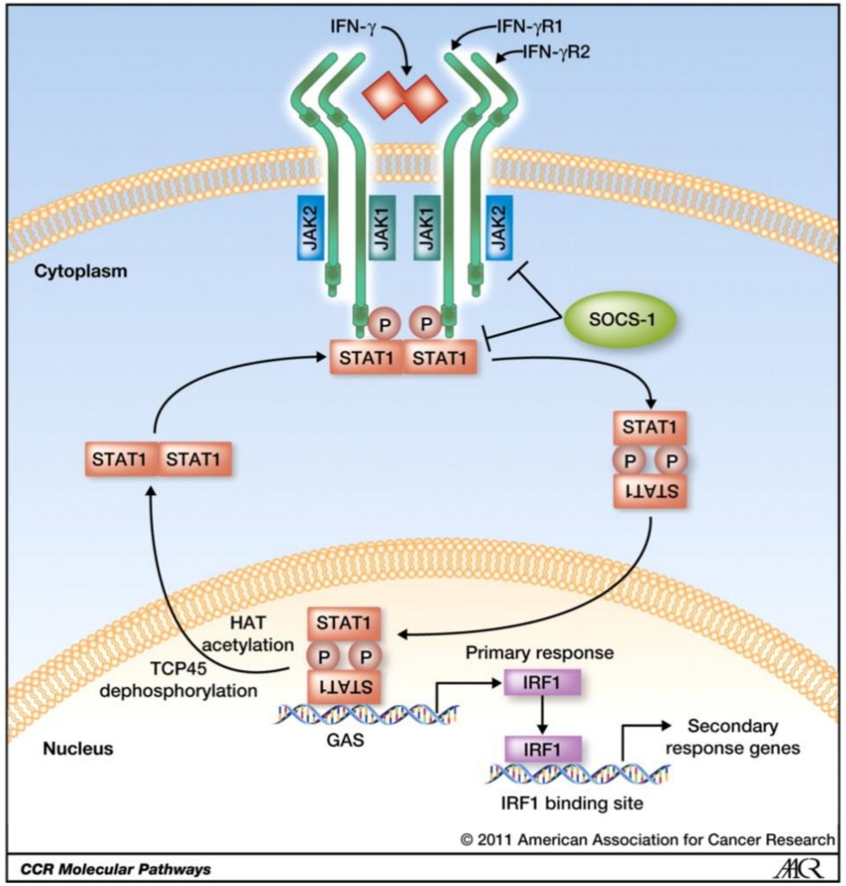


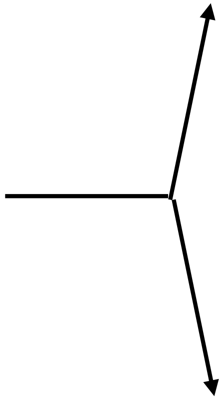
HLA class I loss protects from bystander killing by IFNγ !

IFNγ Signaling Pathway



Zaidi & Merlino, Clin Cancer Res 2011

- enhanced antigen presentation
- proliferation arrest
- apoptosis



anti-tumorigenic

pro-tumorigenic

- checkpoint ligand upregulation (e.g. PD-L1)

Pathway genes

IFNGR1

IFNGR2

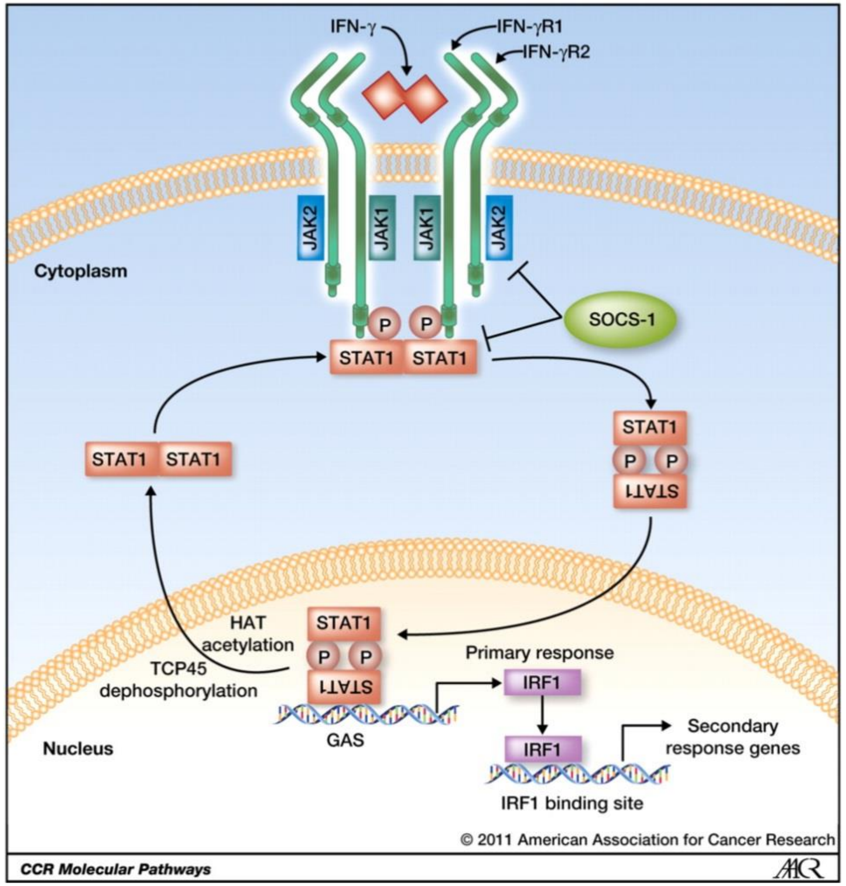
JAK1

JAK2

STAT1

IRF1

IFNγ Signaling Impacts on Patient Survival



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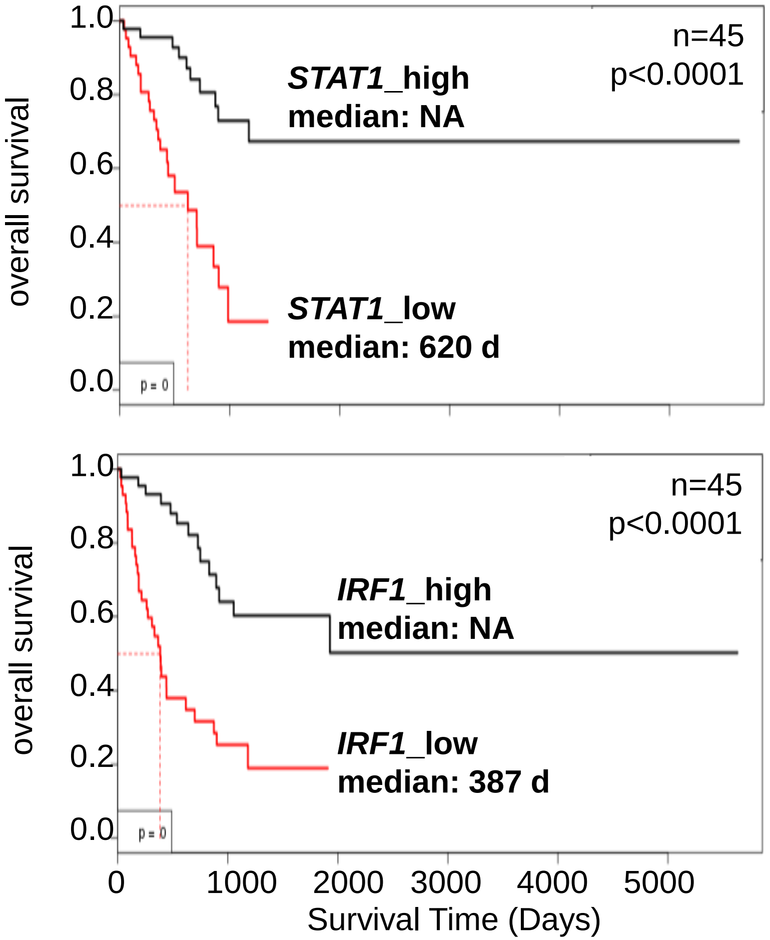

Pathway genes

IFNGR1

IFNGR2

JAK1

JAK2

STAT1

IRF1

Sucker et al., Nat Comm 2017

Patient Ma-Mel-61

year

12/02-03/03 dacarbacine / IFNα — 11/02 cut met, unknown primary melanoma

2003

02/03 LN met

04/03-01/05 IFNα — 03/03 LN mets, 03/03 cut met

07/03 bone mets

11/03 radiatio — 11/03 LN mets

2004

11/03 adrenal met

04/04 cns met

stage IV

2005

01/05 lung mets
01/05 cns met

02/05-04/05 dacarbacine

05/05 cut met
06/05 lung met

08-10/05 gemcitabine / treosulfan — 07/05 cut met

11/05 death

Clinical History of Patient Ma-Mel-61

2002, November:	stage IV melanoma diganosed
2003-2005:	multiple visceral metastases
2005, November:	death

Immunotherapy

2002, Dec. - 2005, Jan:	IFNα

Sucker et al., Nat Comm 2017

Patient Ma-Mel-61

Clinical History of Patient Ma-Mel-61

stage IV

therapy	year	events	cell line
		11/02 cut met unknown primary melanoma	
12/02-03/03 dacarbacine / IFNα	**2003**		
		02/03 LN met	
04/03-01/05 IFNα		03/03 LN mets	→ **Ma-Mel-61a**
		03/03 cut met	→ **Ma-Mel-61b**
		07/03 bone mets	
11/03 radiatio		11/03 LN mets	→ **Ma-Mel-61c**
	2004	11/03 adrenal met	
		04/04 cns met	
	2005		
		01/05 lung mets	→ **Ma-Mel-61e**
		01/05 cns met	
02/05-04/05 dacarbacine			
		05/05 cut met	→ **Ma-Mel-61g**
		06/05 lung met	
08-10/05 gemcitabine / treosulfan		07/05 cut met	→ **Ma-Mel-61h**
		11/05 death	

no response to IFNγ ! (Ma-Mel-61g, Ma-Mel-61h)

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2005, November:	death

Immunotherapy

2002, Dec. - 2005, Jan:	IFNα

Sucker et al., Nat Comm 2017

Patient Ma-Mel-61

stage IV

year

12/02-03/03 dacarbacine / IFNα
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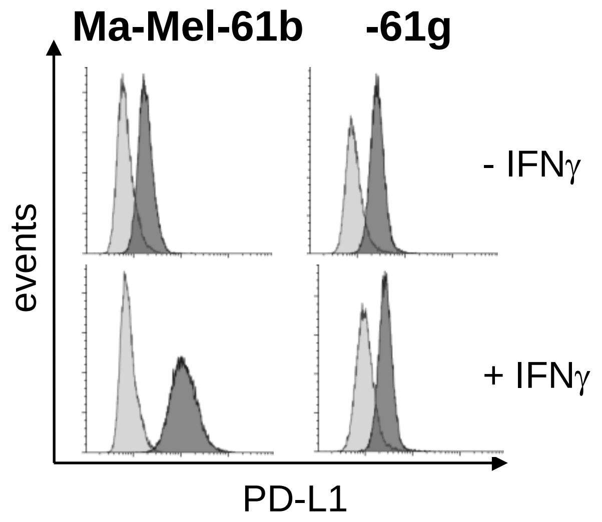
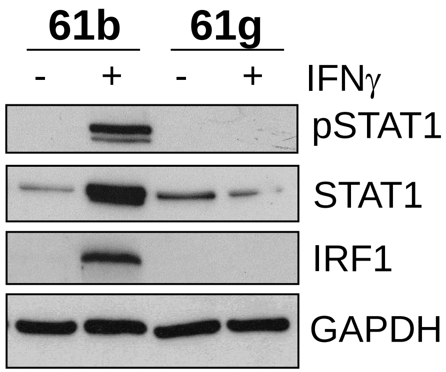
04/03-01/05 IFNα
11/03 radiatio
2004
2005
02/05-04/05 dacarbacine
08-10/05 gemcitabine / treosulfan

11/02 cut met
unknown primary melanoma
02/03 LN met
03/03 LN mets → **Ma-Mel-61a**
03/03 cut met → **Ma-Mel-61b**
07/03 bone mets
11/03 LN mets → **Ma-Mel-61c**
11/03 adrenal met
04/04 cns met
01/05 lung mets → **Ma-Mel-61e**
01/05 cns met
05/05 cut met → **Ma-Mel-61g**
06/05 lung met
07/05 cut met → **Ma-Mel-61h**
11/05 death

JAK1 Mutation in Ma-Mel-61g cells





Sucker et al., Nat Comm 2017

Patient Ma-Mel-61

year

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2003
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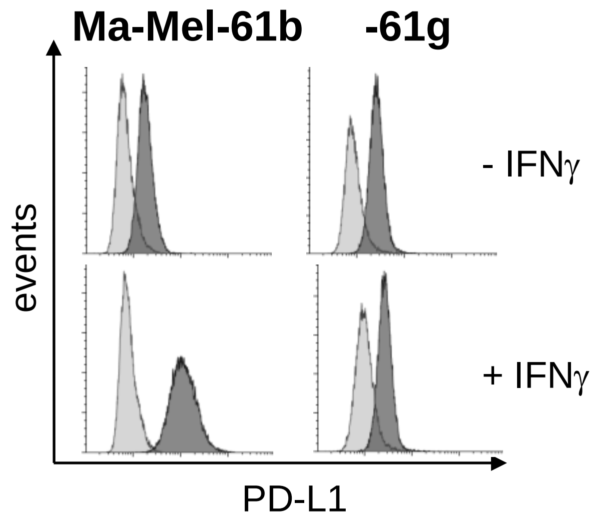
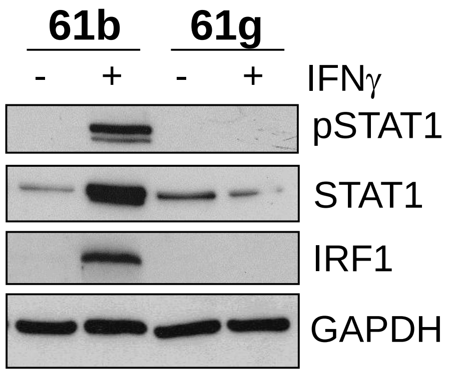
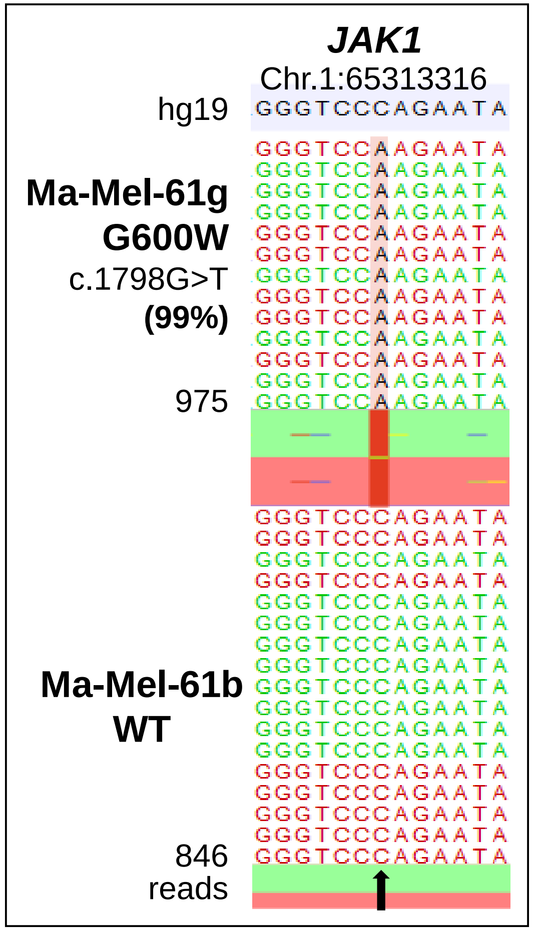
11/05 death

JAK1 Mutation in Ma-Mel-61g cells

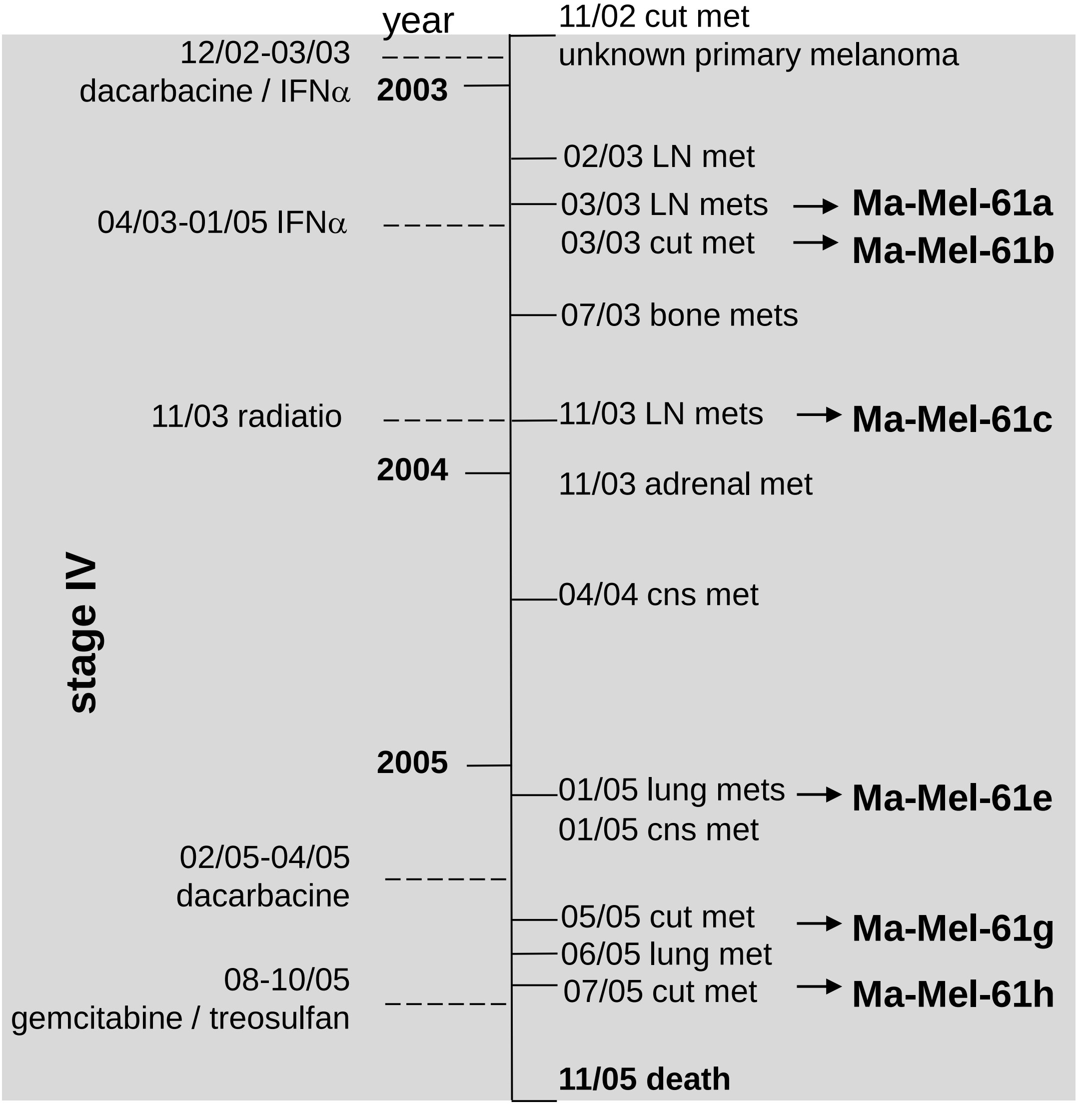




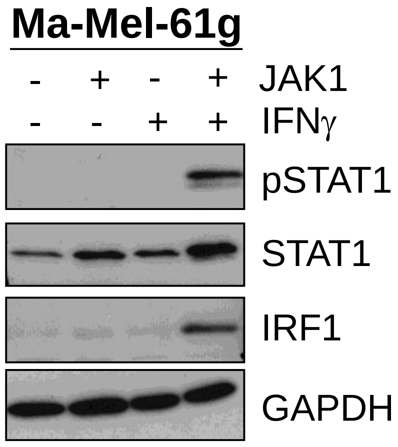


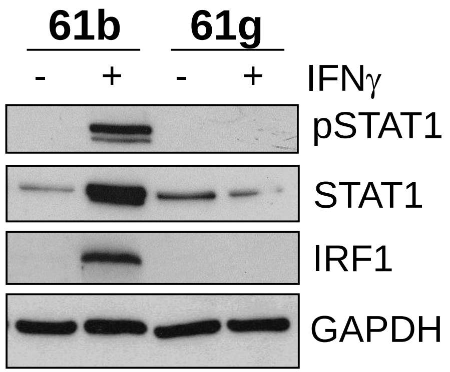
Sucker et al., Nat Comm 2017

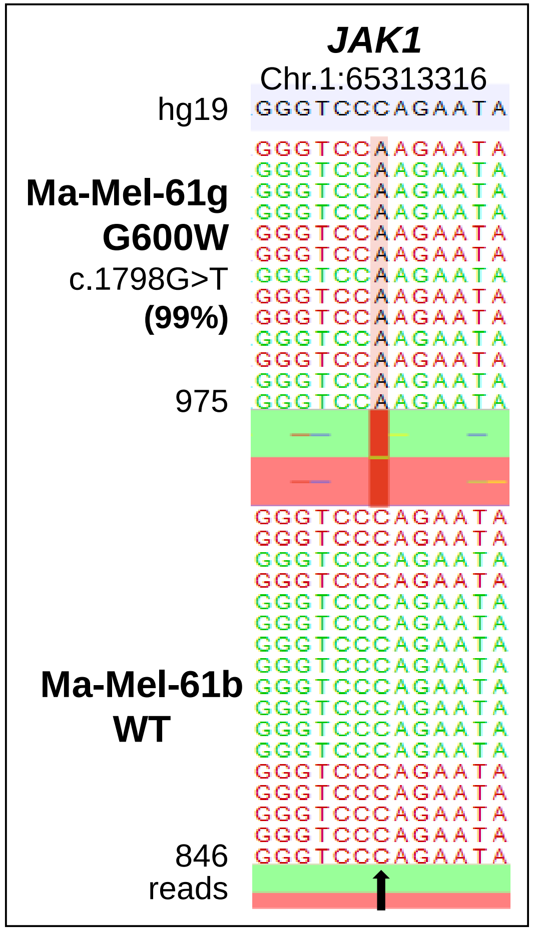
Patient Ma-Mel-61



JAK1 Mutation in Ma-Mel-61g cells







Sucker et al., Nat Comm 2017

Patient Ma-Mel-61

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stage IV
2005
01/05 lung mets → **Ma-Mel-61e**
01/05 cns met
02/05-04/05 dacarbacine
05/05 cut met → **Ma-Mel-61g**
06/05 lung met
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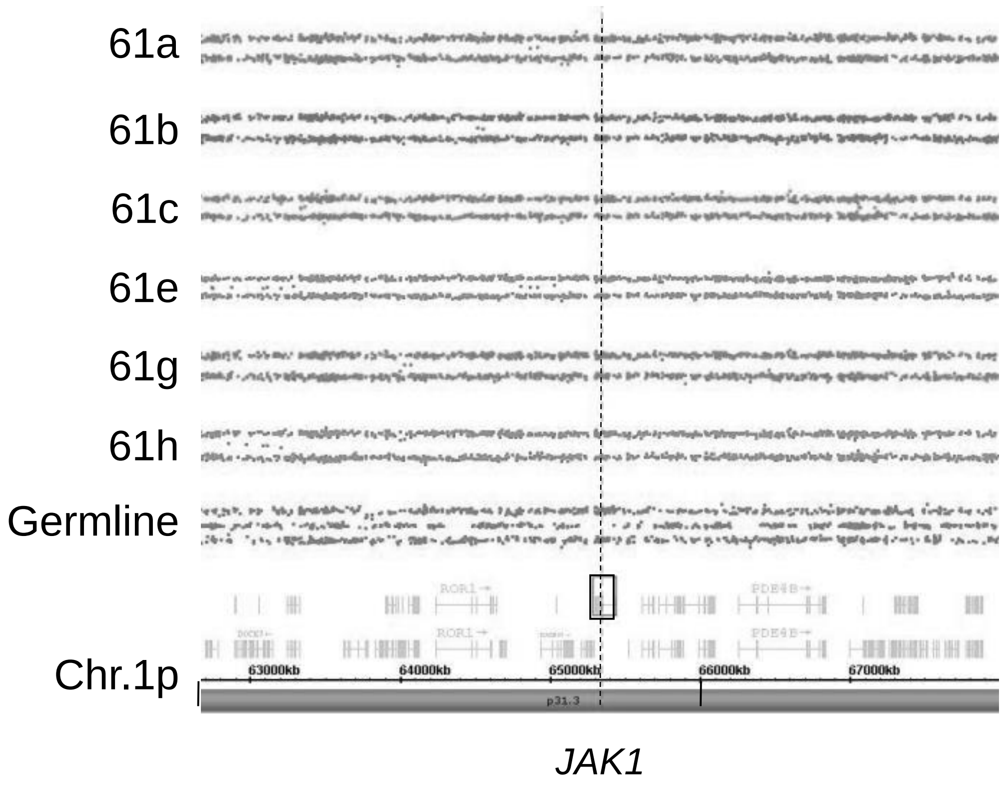
11/05 death

Evolution of JAK1 Deficiency

Allelic distribution



Sucker et al., Nat Comm 2017

Patient Ma-Mel-61

Evolution of JAK1 Deficiency

stage IV

Therapy	year	Event	Cell line
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		02/03 LN met	
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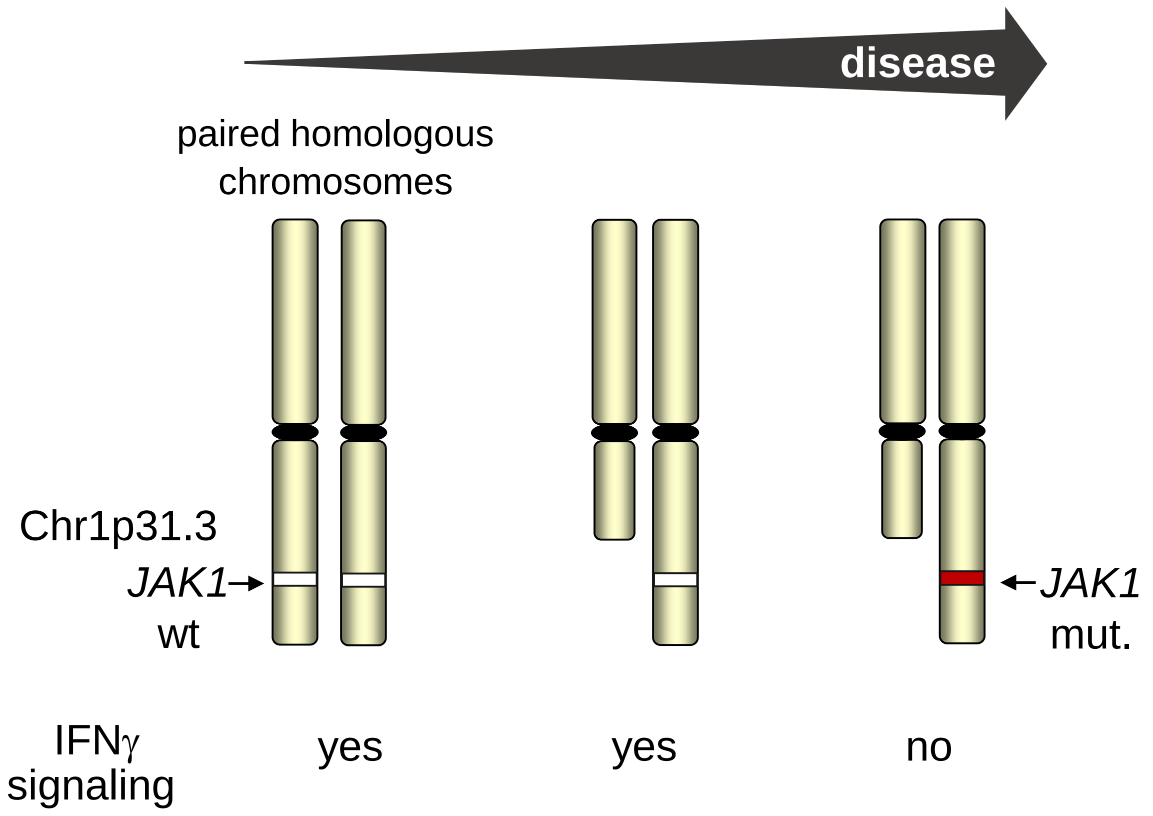
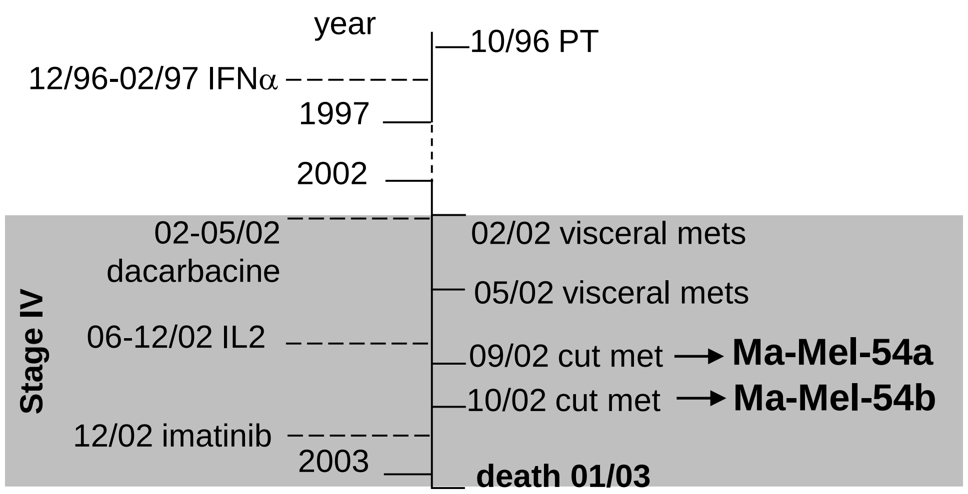
		03/03 cut met	Ma-Mel-61b
		07/03 bone mets	
11/03 radiatio		11/03 LN mets	Ma-Mel-61c
	2004	11/03 adrenal met	
		04/04 cns met	
	2005		
		01/05 lung mets	Ma-Mel-61e
		01/05 cns met	
02/05-04/05 dacarbacine			
		05/05 cut met	Ma-Mel-61g
		06/05 lung met	
08-10/05 gemcitabine / treosulfan		07/05 cut met	Ma-Mel-61h
		11/05 death	



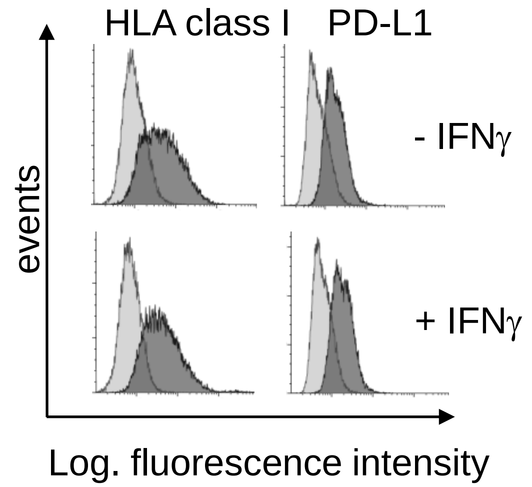
Sucker et al., Nat Comm 2017

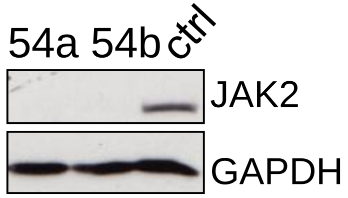
Patient Ma-Mel-54

JAK2 Deficiency in Ma-Mel-54



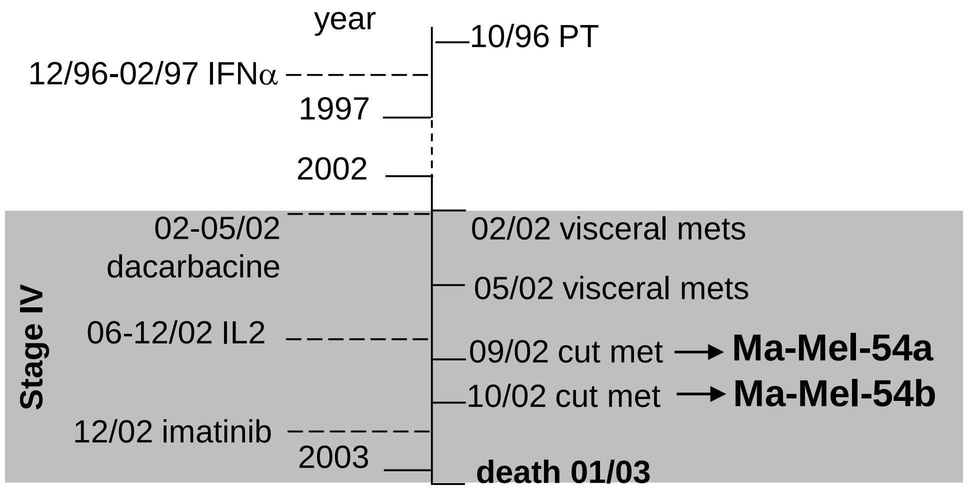
Ma-Mel-54a





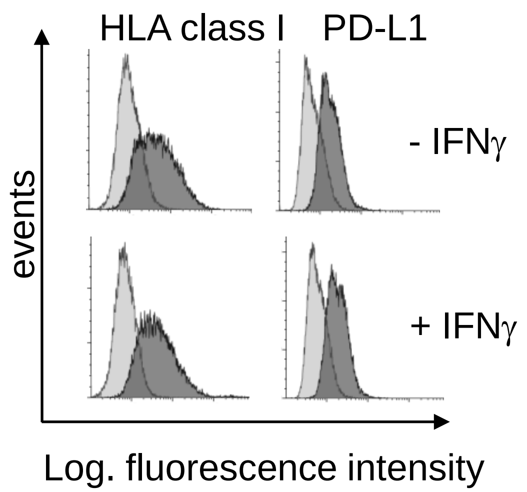
Sucker et al., Nat Comm 2017

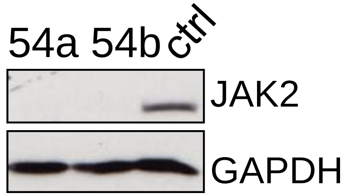
Patient Ma-Mel-54

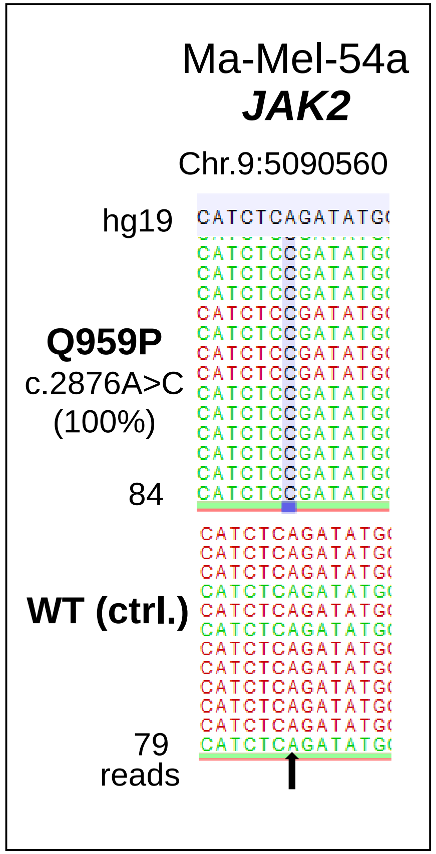


JAK2 Deficiency in Ma-Mel-54

Ma-Mel-54a



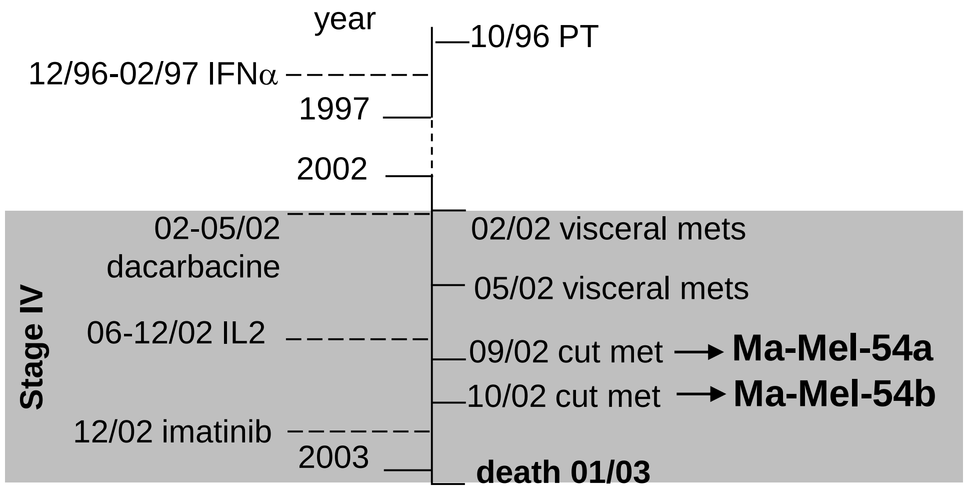




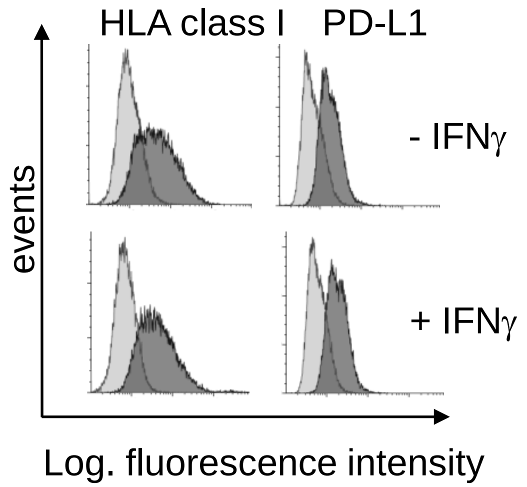
Sucker et al., Nat Comm 2017

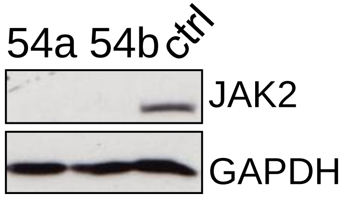
JAK2 Deficiency in Ma-Mel-54

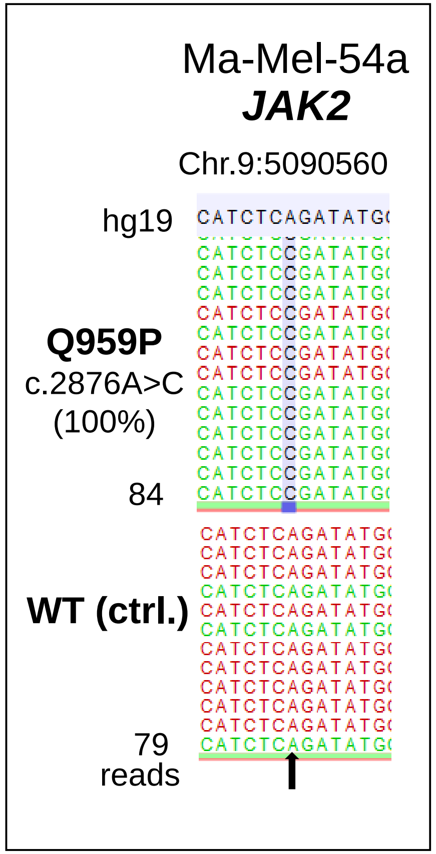
Patient Ma-Mel-54

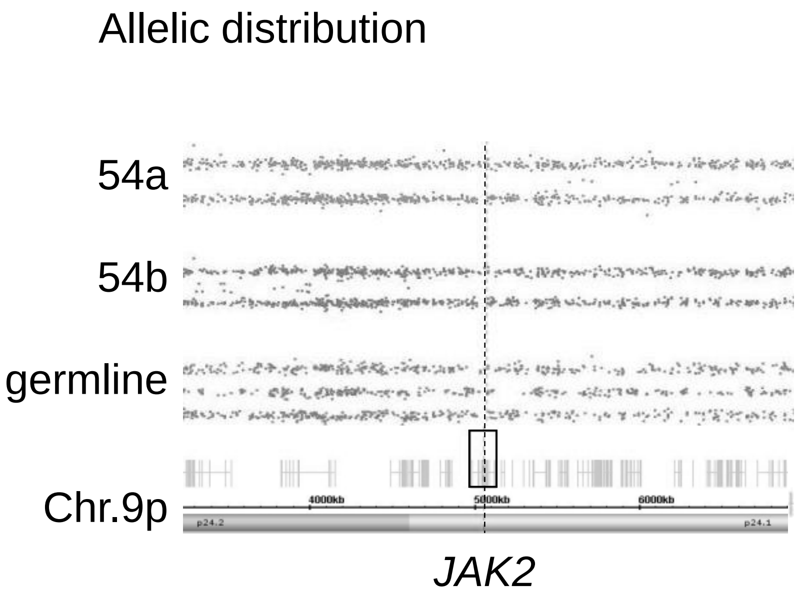


Ma-Mel-54a









Sucker et al., Nat Comm 2017

Frequency of *JAK1/2* Allelic Losses in Melanoma Cells

	Ma-Mel-05	Ma-Mel-08a	Ma-Mel-11	Ma-Mel-12	Ma-Mel-13	Ma-Mel-17	Ma-Mel-19	Ma-Mel-21	Ma-Mel-27	Ma-Mel-30a	Ma-Mel-35	Ma-Mel-36	Ma-Mel-37	Ma-Mel-53	Ma-Mel-59a	Ma-Mel-60	Ma-Mel-61a
JAK1	Not changed	LOH	Not changed	Not changed	Not changed	Not changed	Not changed	Not changed	LOH	LOH	Not changed	LOH	Not changed	Not changed	Not changed	Not changed	LOH
JAK2	LOH	LOH	LOH	LOH	LOH	Not changed	LOH	LOH	LOH	LOH	LOH	LOH	LOH	LOH	LOH	LOH	LOH

	Ma-Mel-62	Ma-Mel-63	Ma-Mel-66a	Ma-Mel-67	Ma-Mel-69	Ma-Mel-71	Ma-Mel-75	Ma-Mel-76	Ma-Mel-79b	Ma-Mel-80a	Ma-Mel-85	Ma-Mel-86a	Ma-Mel-94	Ma-Mel-95	Ma-Mel-101	Ma-Mel-103a	Ma-Mel107
JAK1	Not changed	Not changed	LOH	Not changed	LOH	LOH	Not changed	Not changed	LOH	LOH	Not changed	Not changed	Not changed	Not changed	Not changed	Not changed	Not changed
JAK2	LOH	LOH	LOH	LOH	LOH	Not changed	LOH	LOH	LOH	LOH	Not changed	Not changed	LOH	LOH	LOH	LOH	Not changed

	Ma-Mel-110	Ma-Mel-113	Ma-Mel-114	Ma-Mel-119	Ma-Mel-126	Ma-Mel-128a	Ma-Mel-130	Ma-Mel-134	Ma-Mel-136	Ma-MelKNUD	Ma-Mel-02	Ma-Mel-06	Ma-Mel-10
JAK1	Not changed	Not changed	Not changed	Not changed	Not changed	Not changed	Not changed	Not changed	Not changed	Not changed	Not changed	Not changed	Not changed
JAK2	LOH	Not changed	Not changed	Not changed	Not changed	Not changed	Not changed	LOH	LOH	LOH	LOH	LOH	LOH

	Ma-Mel-23	Ma-Mel-26a	Ma-Mel-32	Ma-Mel-38	Ma-Mel-39a	Ma-Mel-40	Ma-Mel-45a	Ma-Mel-51	Ma-Mel-57	Ma-Mel-58	Ma-Mel-73a	Ma-Mel-150a
JAK1	LOH	LOH	Not changed	LOH	Not changed	Not changed	LOH	Not changed	LOH	Not changed	Not changed	Not changed
JAK2	LOH	LOH	LOH	LOH	LOH	Not changed	LOH	LOH	LOH	Not changed	LOH	Not changed

LOH
Not changed

SNP array data of “in house“ cell lines

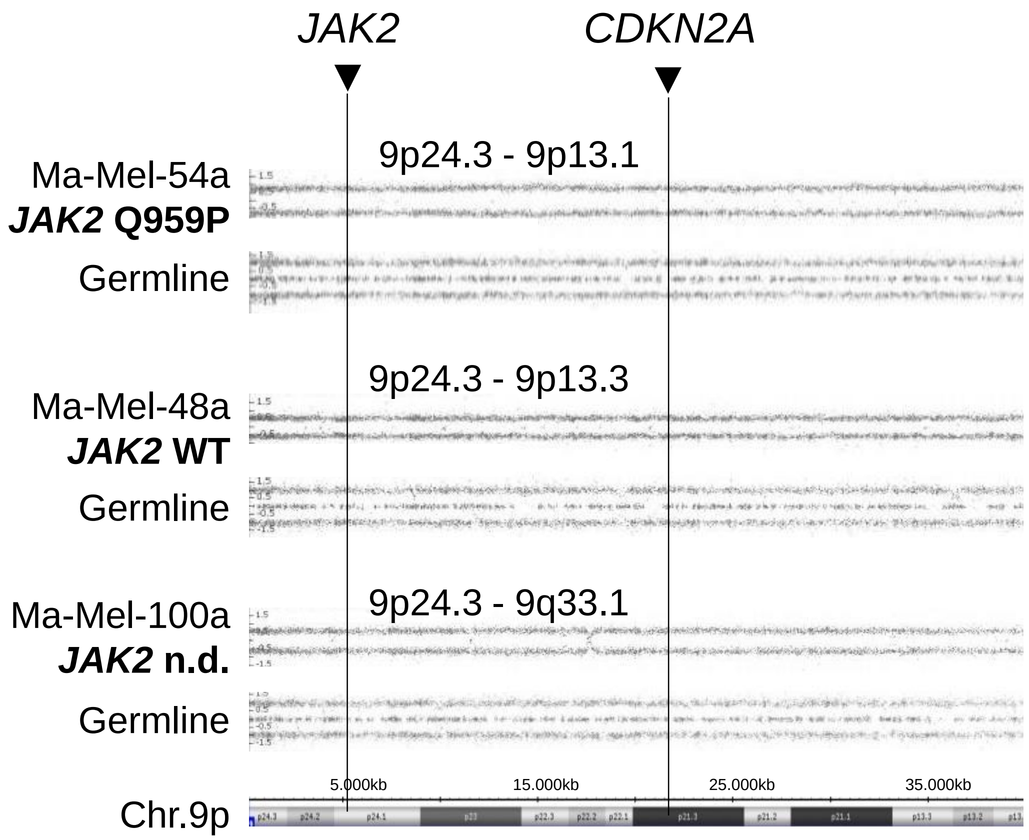
Allelic loss frequency

JAK1: 25% (15 of 59)

JAK2: 76% (45 of 59)

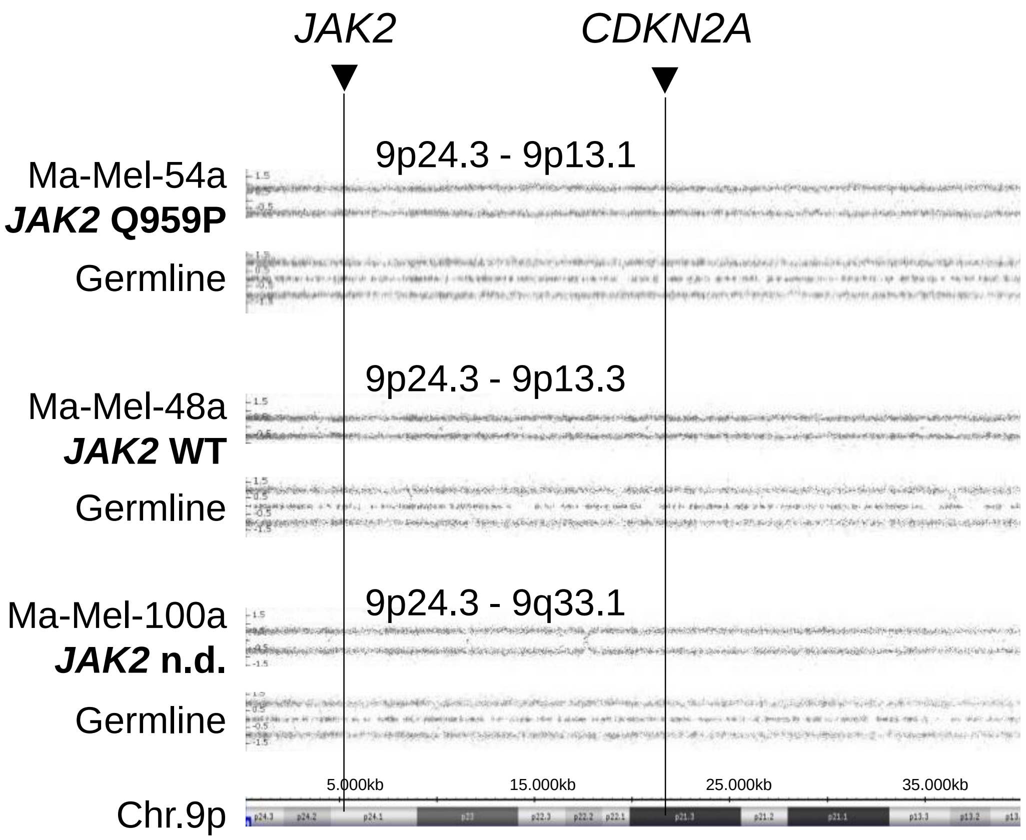
Sucker et al., Nat Comm 2017

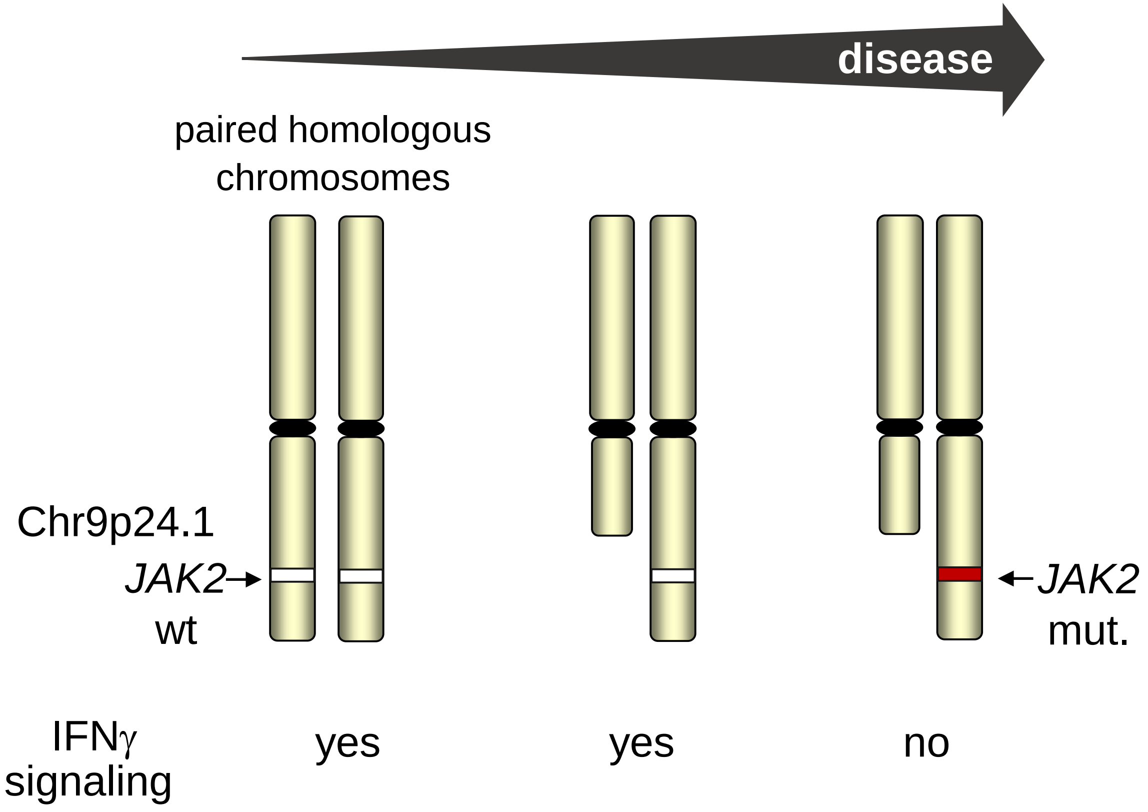
Frequent Codeletion on Chromosome 9p of *JAK2* and *CDKN2A* Alleles



Horn*, Leonardelli* et al., unpublished
*equal contribution

Frequent Codeletion on Chromosome 9p of *JAK2* and *CDKN2A* Alleles





Horn*, Leonardelli* et al., unpublished
*equal contribution

Patient Ma-Mel-61

stage IV

	year		
		11/02 cut met	
12/02-03/03 dacarbacine / IFNα	2003	unknown primary melanoma	
		02/03 LN met	
04/03-01/05 IFNα		03/03 LN mets	→ Ma-Mel-61a
		03/03 cut met	→ Ma-Mel-61b
		07/03 bone mets	
11/03 radiatio		11/03 LN mets	→ Ma-Mel-61c
	2004	11/03 adrenal met	
		04/04 cns met	
	2005		
		01/05 lung mets	→ Ma-Mel-61e
		01/05 cns met	
02/05-04/05 dacarbacine			
		05/05 cut met	→ Ma-Mel-61g
		06/05 lung met	
08-10/05 gemcitabine / treosulfan		07/05 cut met	→ Ma-Mel-61h
		11/05 death	

no response to IFNγ !

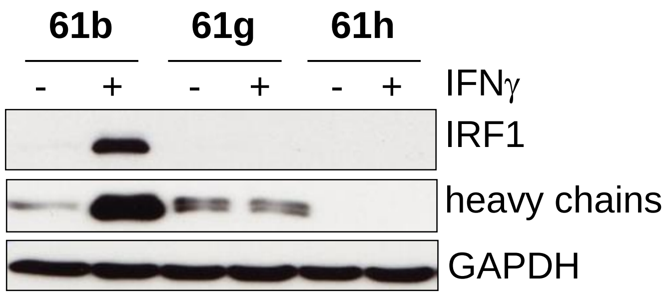
Sucker et al., Nat Comm 2017

Patient Ma-Mel-61

stage IV

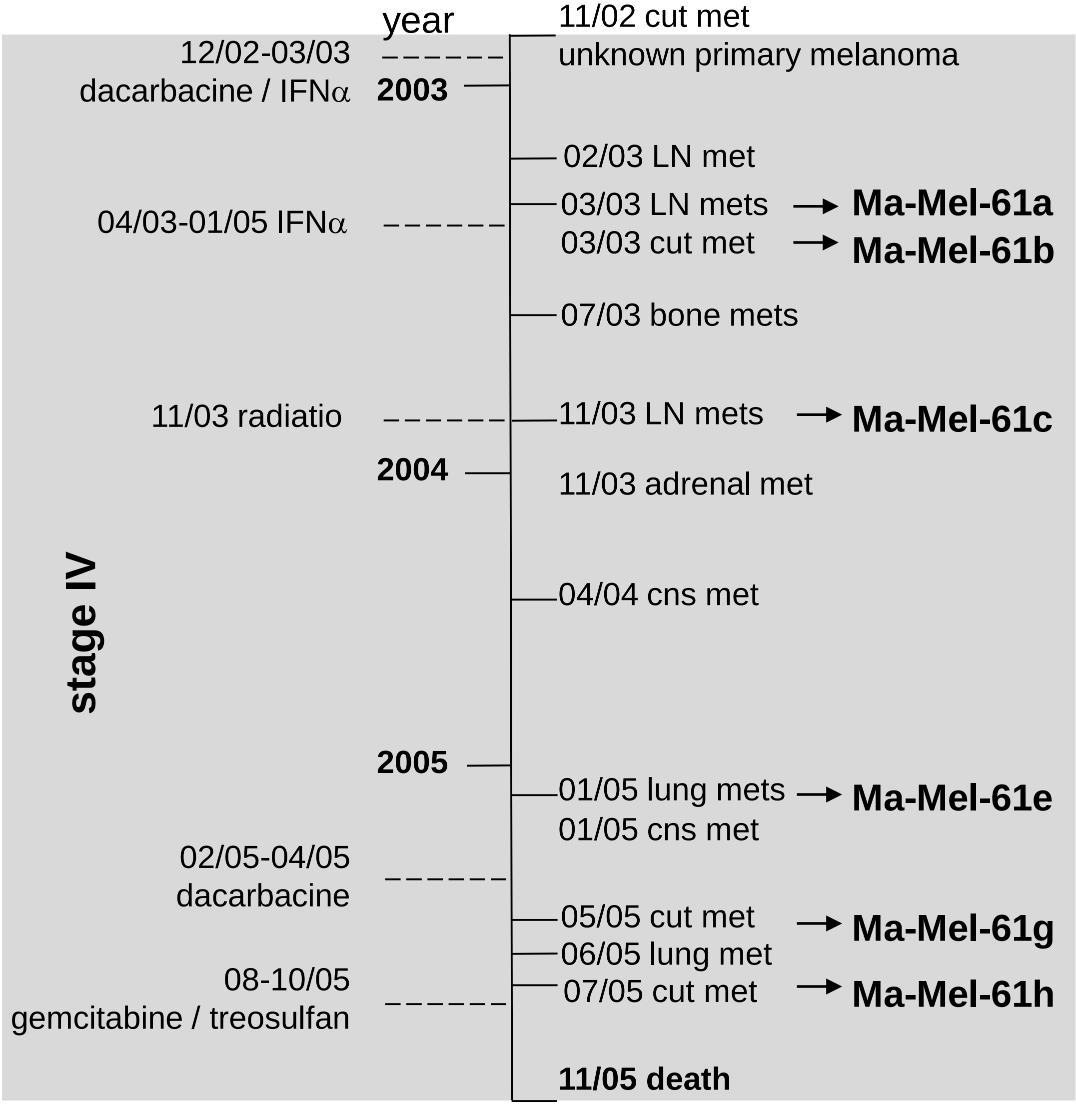
	year	
		11/02 cut met
12/02-03/03 dacarbacine / IFNα		unknown primary melanoma
	2003	
		02/03 LN met
04/03-01/05 IFNα		03/03 LN mets → **Ma-Mel-61a**
		03/03 cut met → **Ma-Mel-61b**
		07/03 bone mets
11/03 radiatio		11/03 LN mets → **Ma-Mel-61c**
	2004	
		11/03 adrenal met
		04/04 cns met
	2005	
		01/05 lung mets → **Ma-Mel-61e**
		01/05 cns met
02/05-04/05 dacarbacine		
		05/05 cut met → **Ma-Mel-61g**
		06/05 lung met
08-10/05 gemcitabine / treosulfan		07/05 cut met → **Ma-Mel-61h**
		11/05 death

Lack of HLA class I Expression on Ma-Mel-61h

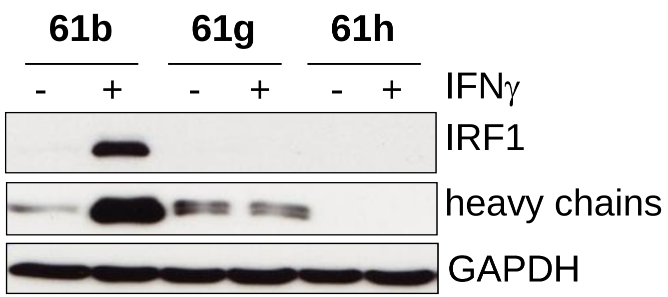


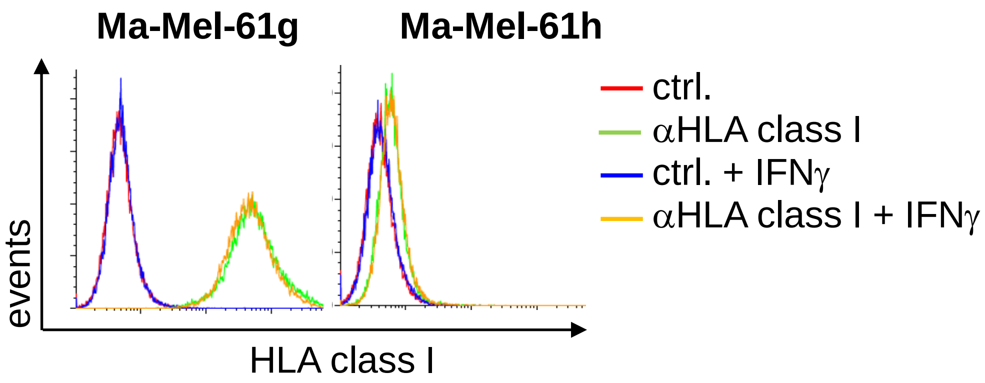
Sucker et al., Nat Comm 2017

Patient Ma-Mel-61



Lack of HLA class I Expression on Ma-Mel-61h





Sucker et al., Nat Comm 2017

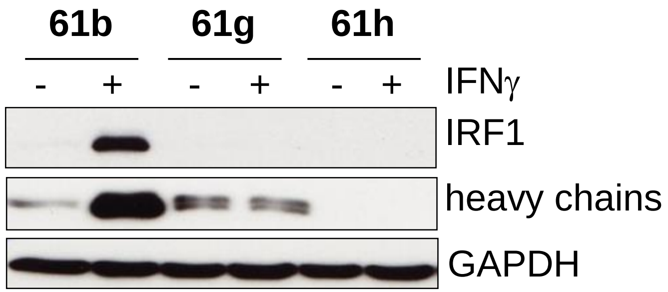
Patient Ma-Mel-61

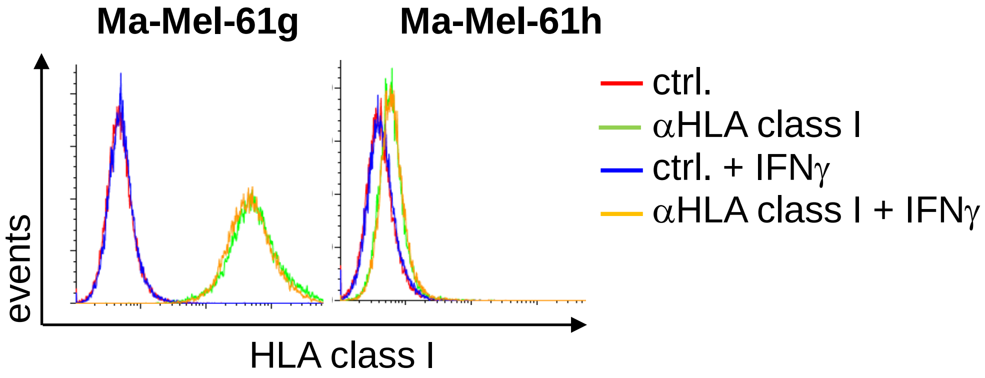
year

12/02-03/03 dacarbacine / IFNα ------ | 11/02 cut met unknown primary melanoma
2003
02/03 LN met
04/03-01/05 IFNα ------ | 03/03 LN mets → **Ma-Mel-61a**
03/03 cut met → **Ma-Mel-61b**
07/03 bone mets
11/03 radiatio ------ | 11/03 LN mets → **Ma-Mel-61c**
2004
11/03 adrenal met
04/04 cns met
2005
01/05 lung mets → **Ma-Mel-61e**
01/05 cns met
02/05-04/05 dacarbacine ------
05/05 cut met → **Ma-Mel-61g**
06/05 lung met
08-10/05 gemcitabine / treosulfan ------ | 07/05 cut met → **Ma-Mel-61h**
11/05 death

stage IV

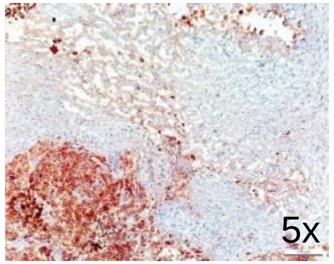
Lack of HLA class I Expression on Ma-Mel-61h



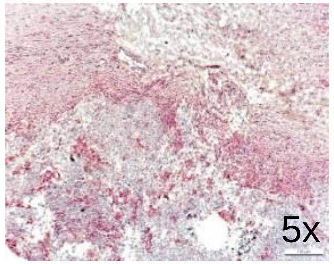


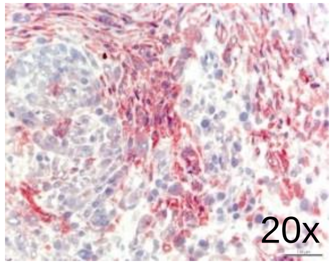
Ma-Mel-61g

HMB45



HLA class I





Sucker et al., Nat Comm 2017

Patient Ma-Mel-61

year

stage IV

12/02-03/03 dacarbacine / IFNα — 11/02 cut met, unknown primary melanoma

2003

02/03 LN met

04/03-01/05 IFNα — 03/03 LN mets → **Ma-Mel-61a**

03/03 cut met → **Ma-Mel-61b**

07/03 bone mets

11/03 radiatio — 11/03 LN mets → **Ma-Mel-61c**

2004

11/03 adrenal met

04/04 cns met

2005

01/05 lung mets → **Ma-Mel-61e**

01/05 cns met

02/05-04/05 dacarbacine

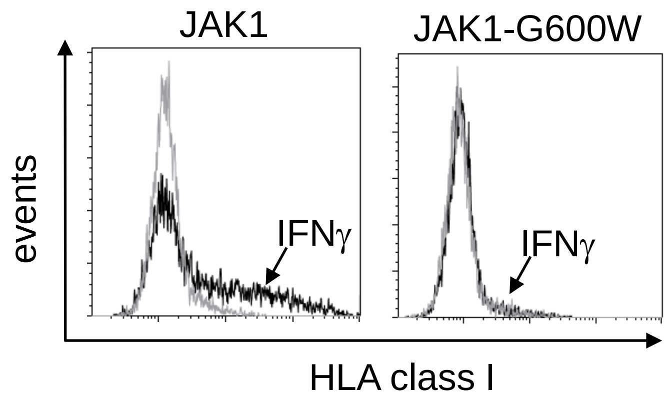
05/05 cut met → **Ma-Mel-61g**

06/05 lung met

08-10/05 gemcitabine / treosulfan — 07/05 cut met → **Ma-Mel-61h**

11/05 death

Silencing of Antigen Presentation Genes



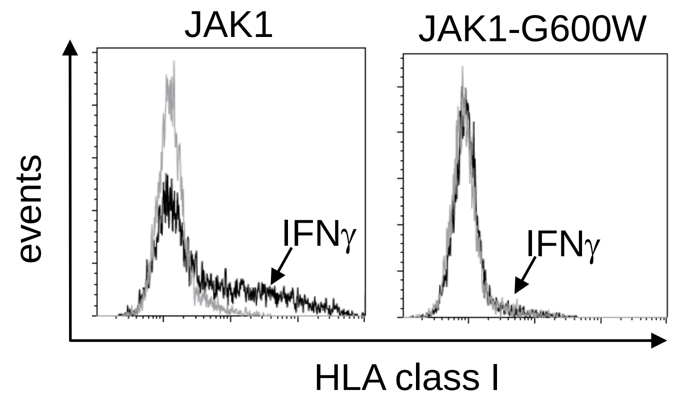
Sucker et al., Nat Comm 2017

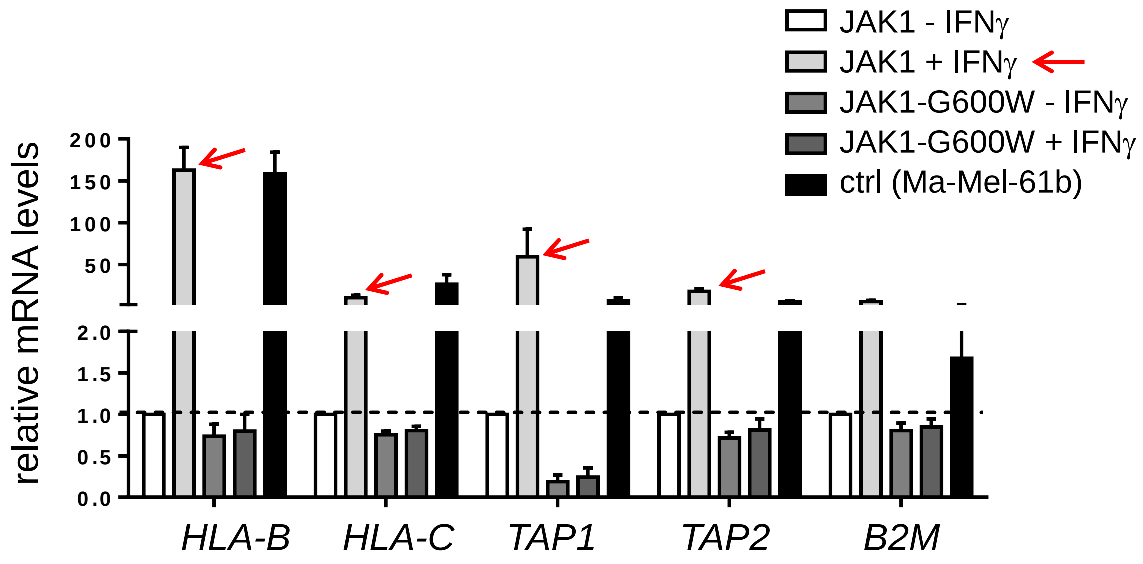
Patient Ma-Mel-61

Silencing of Antigen Presentation Genes

stage IV

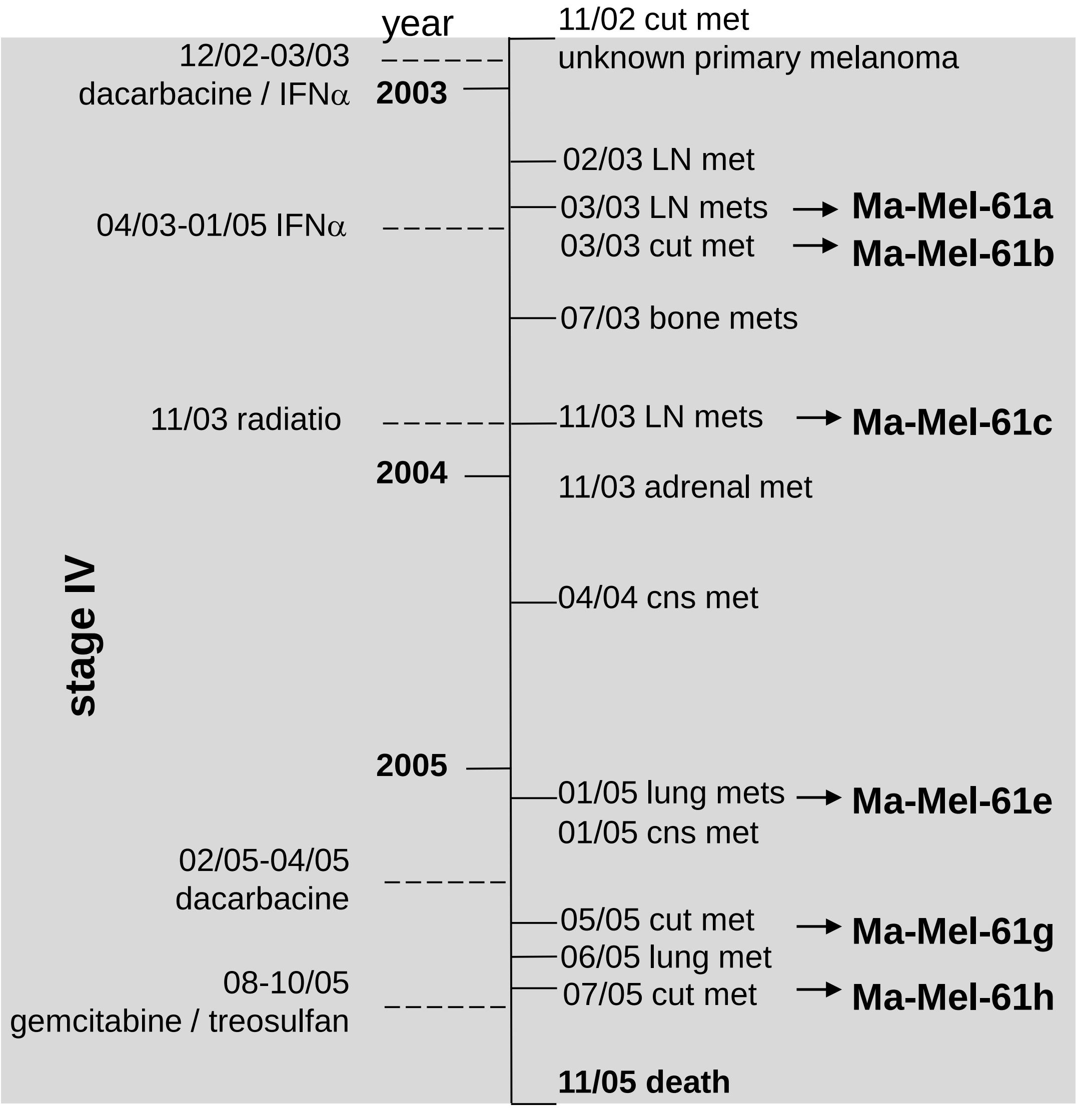
Therapy	year	Events
		11/02 cut met unknown primary melanoma
12/02-03/03 dacarbacine / IFNα	**2003**	
		02/03 LN met
04/03-01/05 IFNα		03/03 LN mets → **Ma-Mel-61a**
		03/03 cut met → **Ma-Mel-61b**
		07/03 bone mets
11/03 radiatio		11/03 LN mets → **Ma-Mel-61c**
	2004	11/03 adrenal met
		04/04 cns met
	2005	
		01/05 lung mets → **Ma-Mel-61e**
		01/05 cns met
02/05-04/05 dacarbacine		
		05/05 cut met → **Ma-Mel-61g**
		06/05 lung met
08-10/05 gemcitabine / treosulfan		07/05 cut met → **Ma-Mel-61h**
		11/05 death



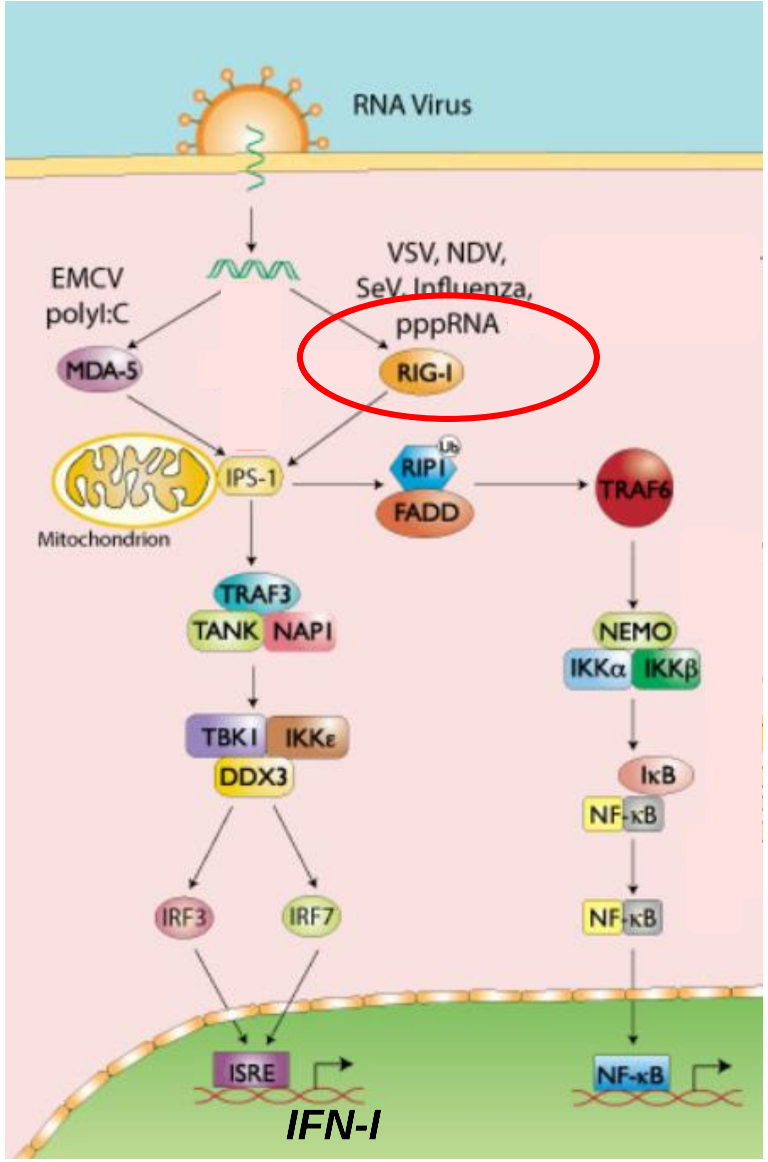


Sucker et al., Nat Comm 2017

Patient Ma-Mel-61



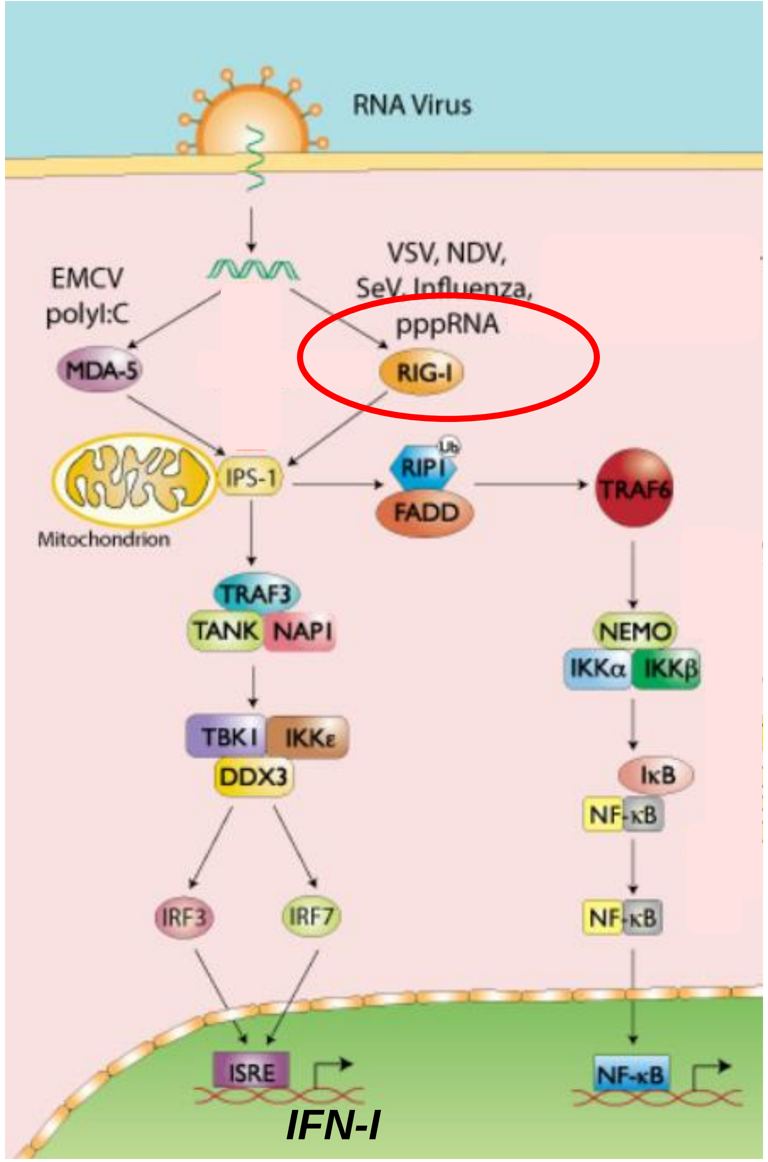
How to restore HLA class I antigen presentation in Ma-Mel-61h?



adapted from
http://www.invivogen.com/review-rlr

RIG-I (retinoic acid inducible gene I)

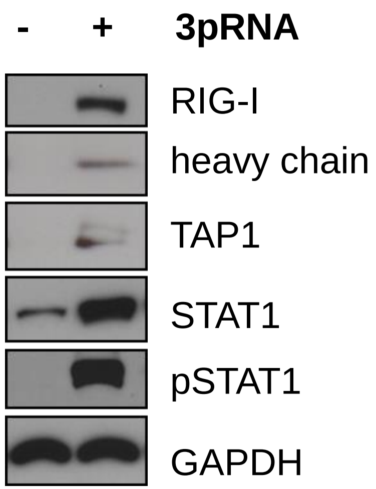
- Ubiquitious innate cytosolic pattern recognition receptor
- RNA helicase binds short double-stranded viral pppRNA
- RIG-I activation in tumor cells by transfection with synthetic 3pRNA



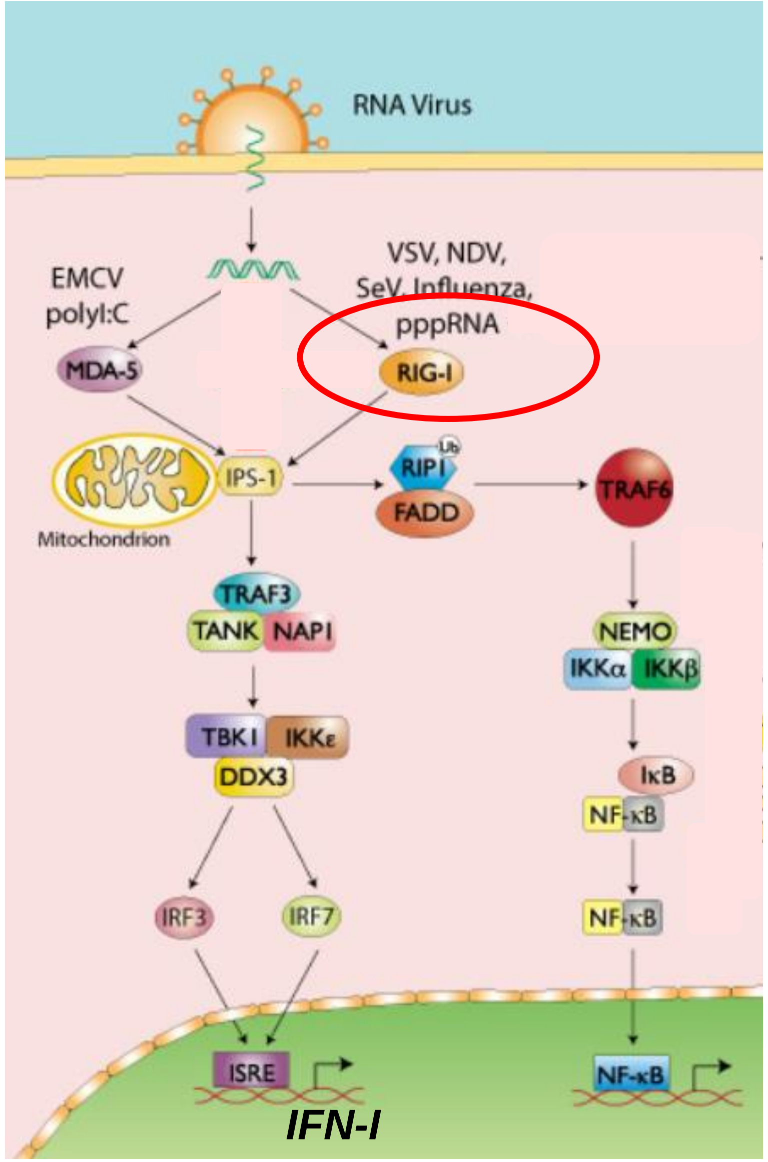
adapted from
http://www.invivogen.com/review-rlr

RIG-I Signaling Restores HLA class I Expression

Ma-Mel-61h
(JAK1-G600W)



Such et al., unpublished



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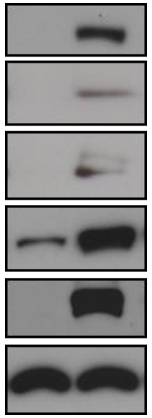
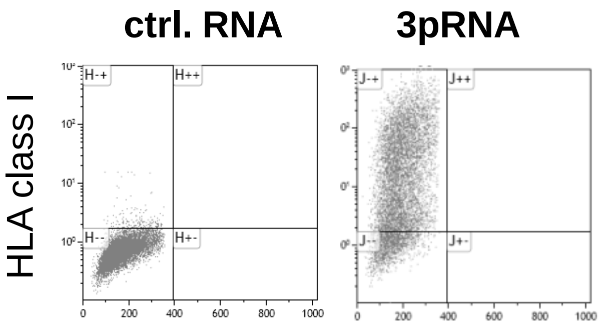
RIG-I Signaling Restores HLA class I Expression

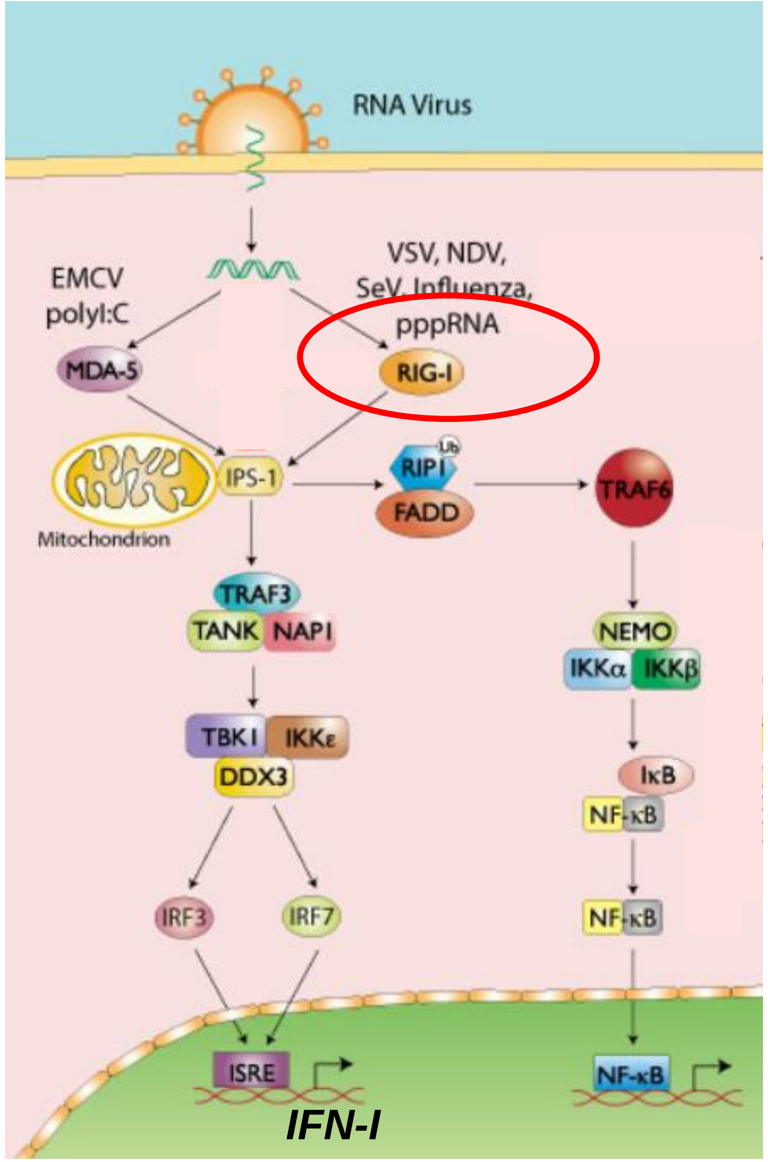
Ma-Mel-61h
(JAK1-G600W)





Such et al., unpublished

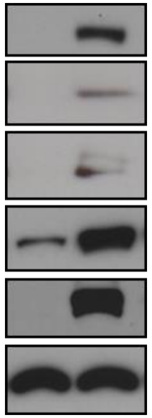
RIG-I Signaling Restores HLA class I Expression



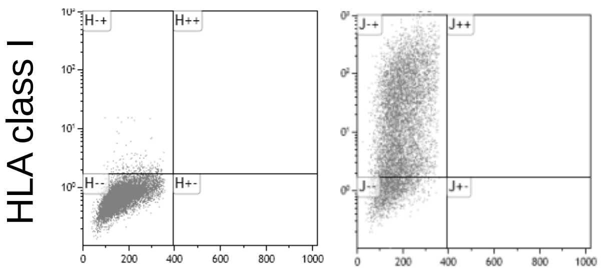
adapted from
http://www.invivogen.com/review-rlr

Ma-Mel-61h (JAK1-G600W)

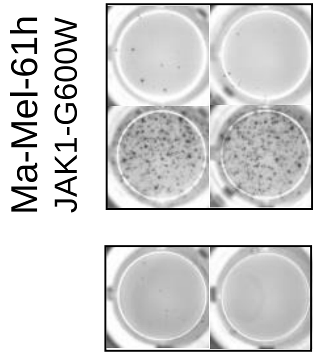
- + 3pRNA



RIG-I
heavy chain
TAP1
STAT1
pSTAT1
GAPDH



auto. CD8+ T cells



Such et al., unpublished

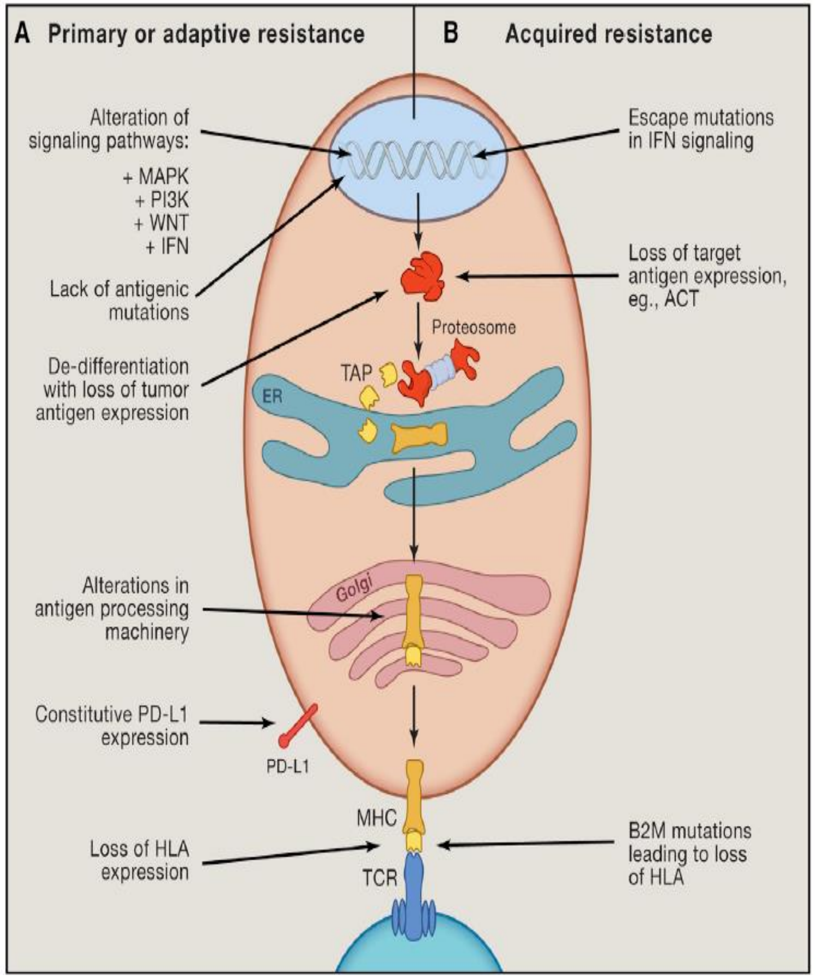
Multiple Acquired Resistance Mechanisms in Ma-Mel-61 and Ma-Mel-54

- Acquired IFNγ resistance due to chromosomal aberrations and concomitant inactivation of *JAK1/2* genes

- T cell resistance due to silencing of genes involved in antigen presentation

- RIG-I activation in tumor cells overcomes silencing of antigen presentation genes in IFN-resistant melanoma cells and re-sensitizes tumor cells to autologous $CD8^+$ T cells

Resistance mechanisms



Sharma et al., *Cell* 2017

IFNγ pathway mutations

Zaretsky *et al., NEJM* 2016	Melanoma - ICB
Gao et al., *Cell* 2016	Melanoma - ICB
Shin et al., *Cancer Discov* 2017	Melanoma - ICB
Sucker et al., *Nat Commun* 2017	Melanoma – non-ICB

Loss of neoantigen expression

Anagnostou *et al., Cancer Discov* 2017	Lung

HLA haplotype loss

McGranahan et al., *Cell 2017*	Lung - ICB
Zhao et al., *Cancer Res* 2016	Melanoma - non-ICB

B2M deficiency

Zaretsky *et al. NEJM* 2016	Melanoma - ICB
Gettinger et al., *Cancer Discov 2017*	Lung - ICB
Sade-Feldman et al., *Nat Commun 2017*	Melanoma - ICB
Zhao et al., *Cancer Res* 2016	Melanoma – non-ICB
Sucker et al., *Clin Cancer Res 2014*	Melanoma – non-ICB

Take home message

- Early chromosomal aberrations predispose to acquired IFNγ resistance and T cell resistance in melanoma

- Screening of patient metastases for chromosomal aberration and gene mutations prior to immunotherapy to define the risk of resistance development

Contributors

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Soldano Ferrone

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