



Genomics and Proteomics in Immunotherapy Trials

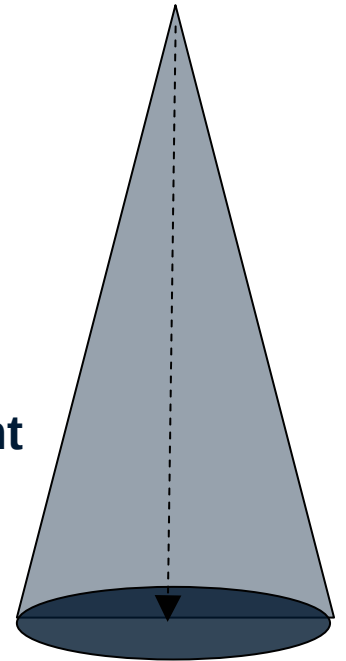
iSBTc 19th Annual Meeting
Immune Monitoring Workshop
San Francisco, Nov 4th 2004

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Bethesda MD

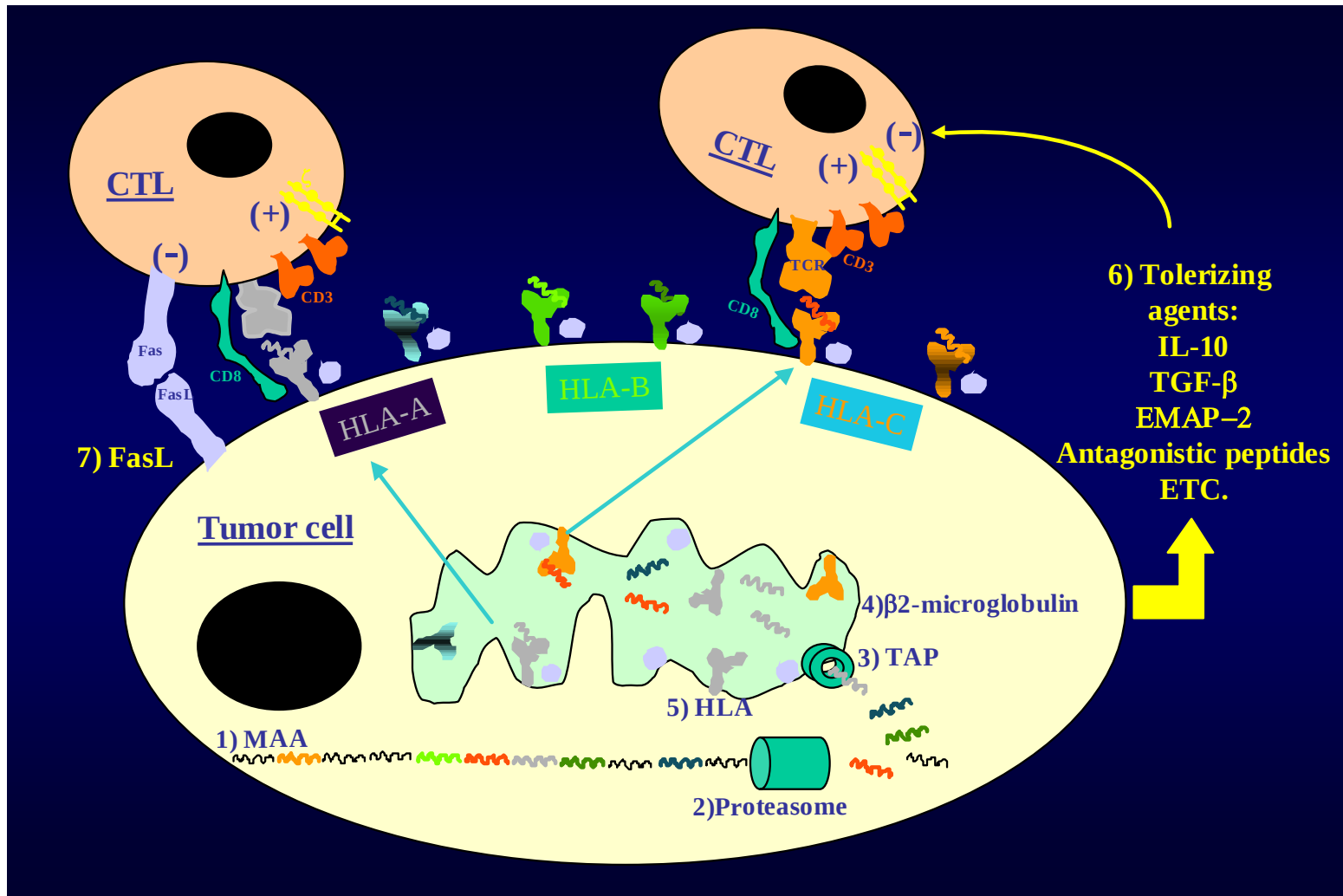


Multidimensionality of tumor/host interactions in the context of T cell aimed immunization

- 1st dimension = TCR/HLA/epitope interaction**
- 2nd dimension = Importance of co-stimulation**
- 3rd dimension = Localization at tumor site**
- 4th dimension = Evolving nature of immune response and
genetic instability of cancer cells**
- 5th dimension = Heterogeneity of the tumor micro-environment**



T cell recognition of cancer cells



Multidimensionality of tumor/host interactions in the context of T cell aimed immunization

1st dimension = TCR/HLA/epitope interaction

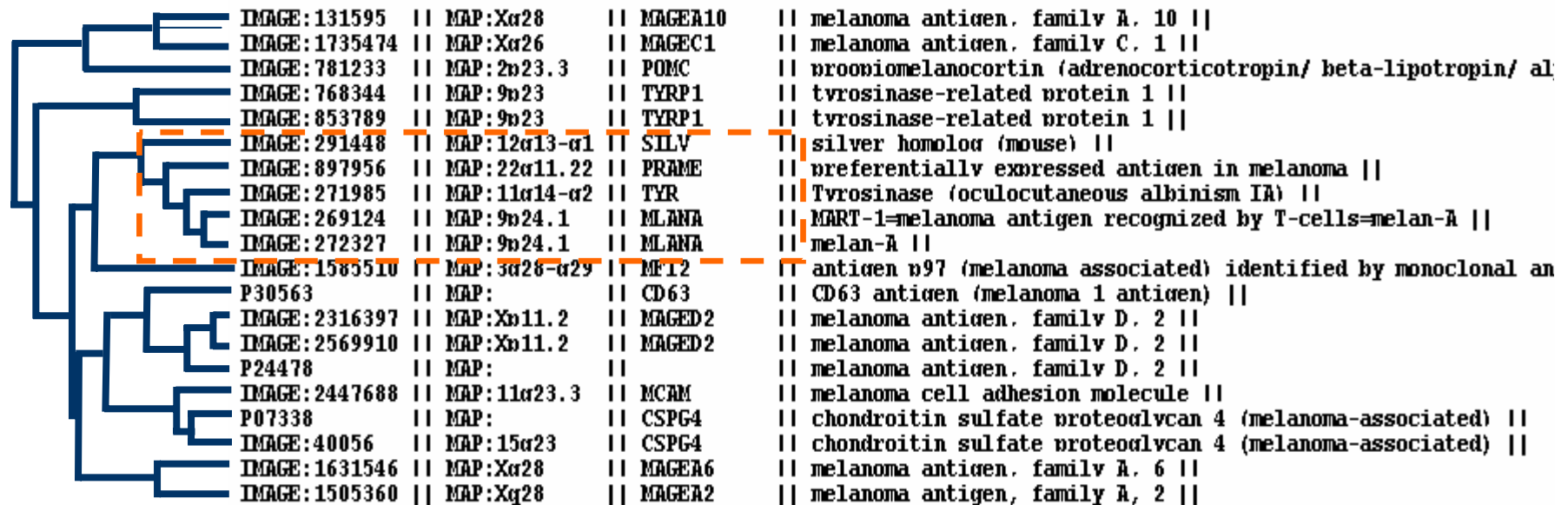
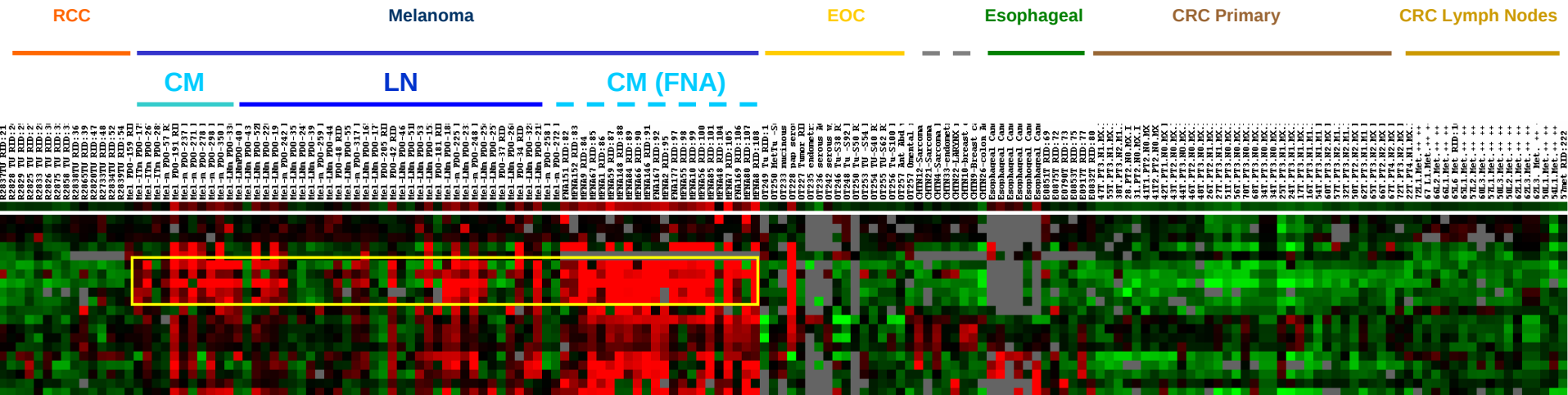
2nd dimension = Importance of co-stimulation

3rd dimension = Localization at tumor site

**4th dimension = Evolving nature of immune response and
genetic instability of cancer cells**

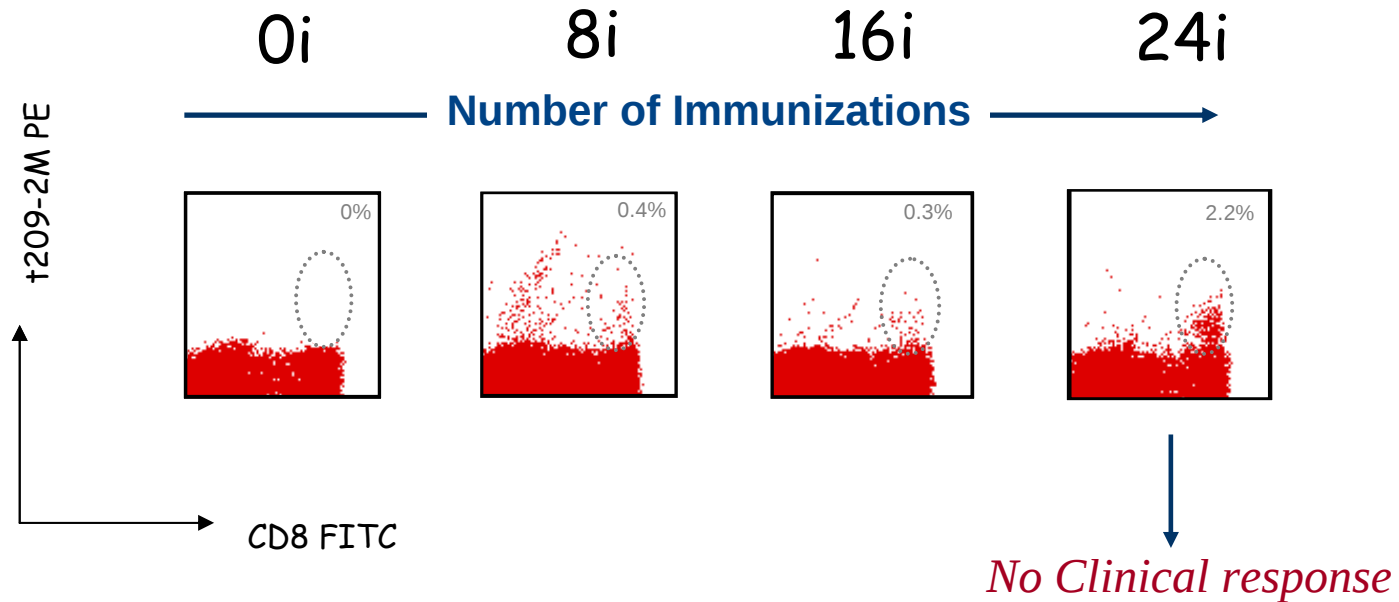
5th dimension = Heterogeneity of the tumor micro-environment

Most commonly expressed melanoma associated antigens



The Systemic Response

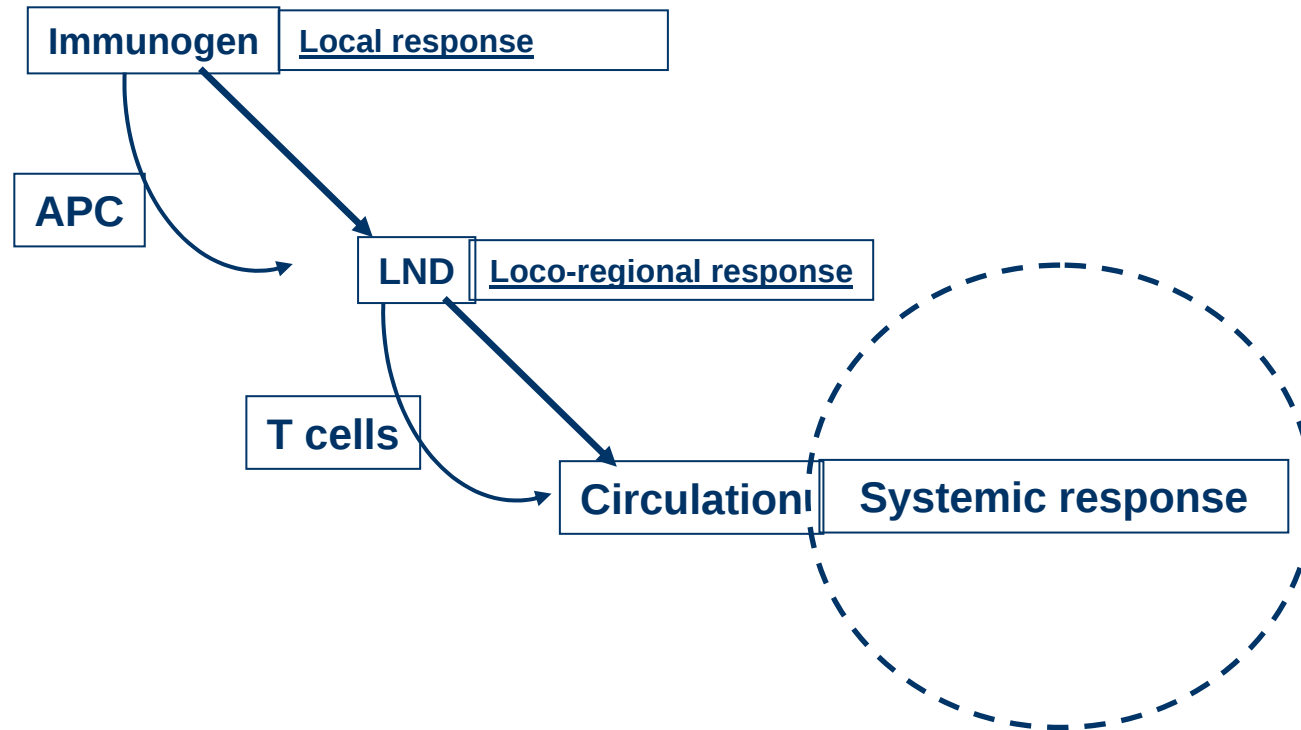
Model: g209-2M peptide vaccine $\pm$ interleukin-2



Lee et al. J. Immunol. 1999,
Kammula et al, 1999
Nielsen et al. J Immunol 2000

Monsurró et al. J Immunol 2000
Kammula et al. J Natl Canc Inst 2002
Monsurró et al., J Immunol 2002

Few logical steps required for successful anti-cancer immunization



Multidimensionality of tumor/host interactions in the context of T cell aimed immunization

1st dimension = TCR/HLA/peptide interaction

2nd dimension = Importance of co-stimulation

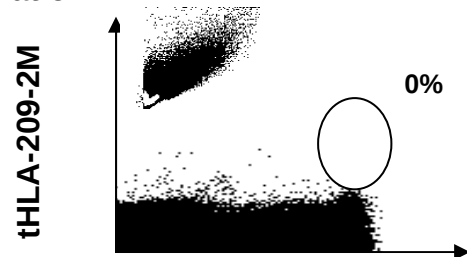
3rd dimension = Localization at tumor site

**4th dimension = Evolving nature of immune response and
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5th dimension = Heterogeneity of the tumor micro-environment

Functional heterogeneity of vaccine-induced CD8+ T cells

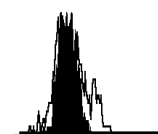
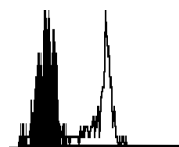
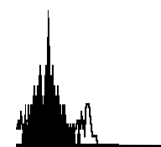
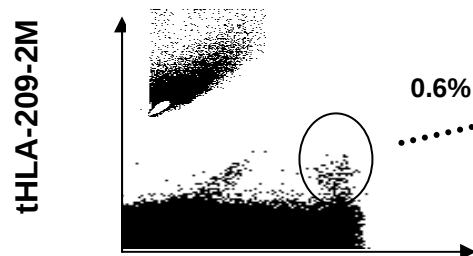
Pre-vaccination



CD8

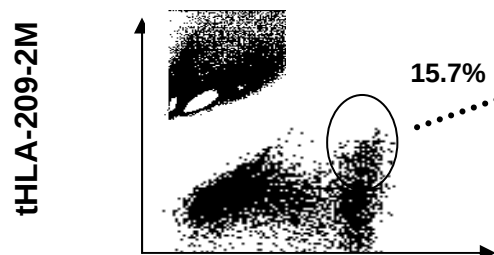
Classic effector phenotype

Post-vaccination

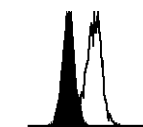
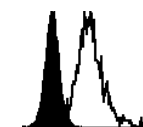


CD8

Post-vaccination
After IVS/209-2M

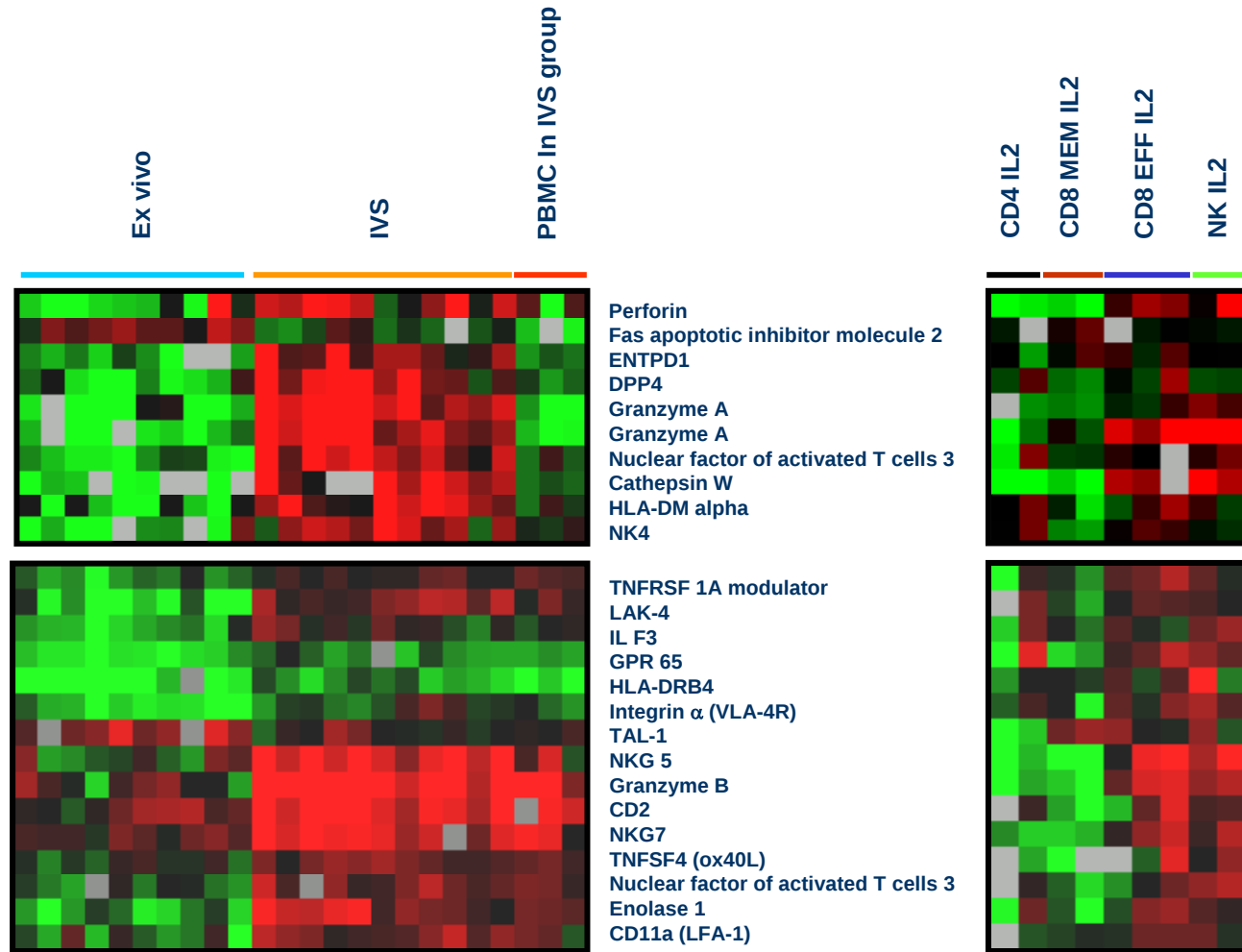


CD8

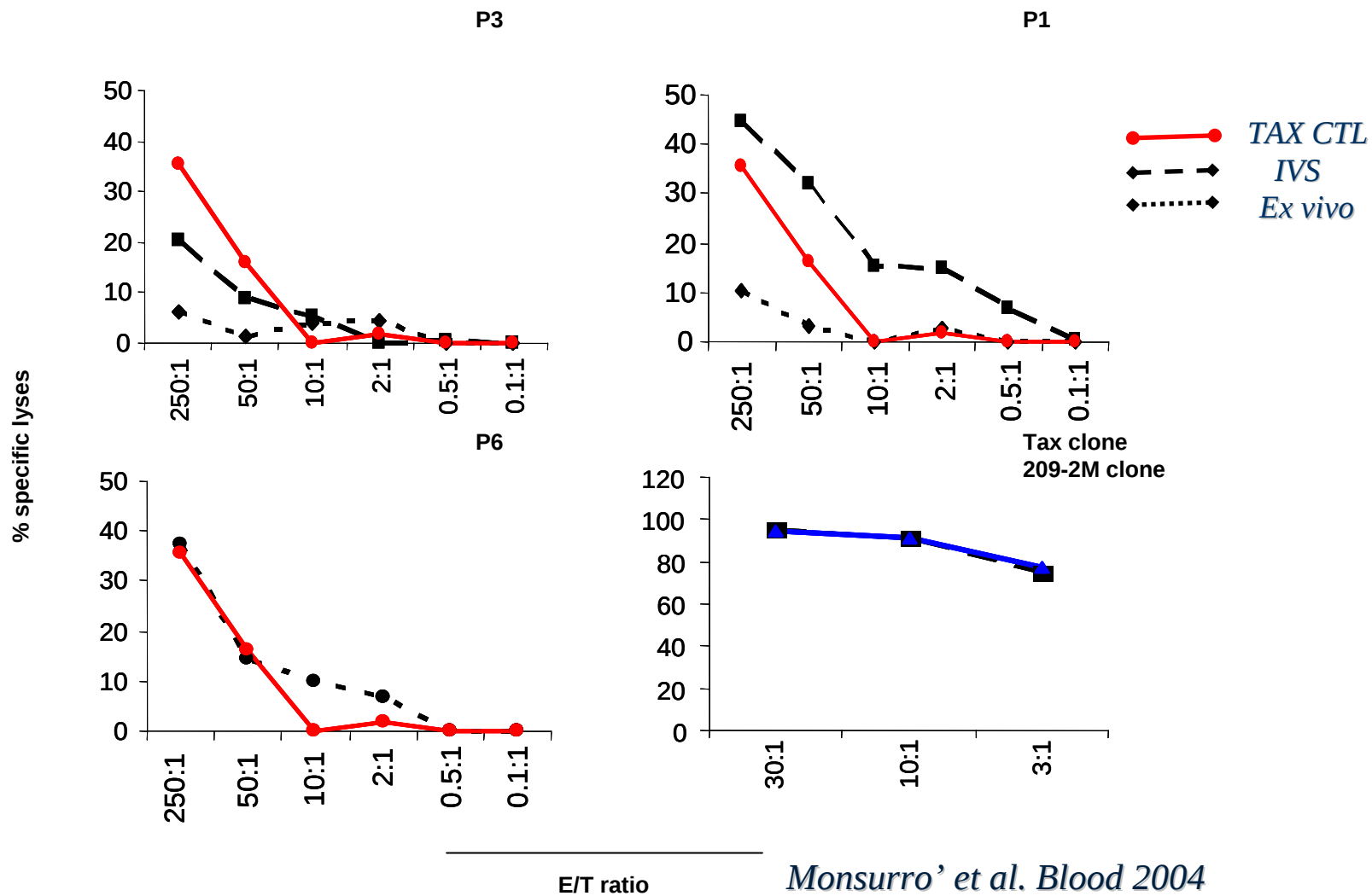


Monsurro' et al. J Immunol 2002

Quiescent phenotype of tumor-specific CD8+ T cells following immunization

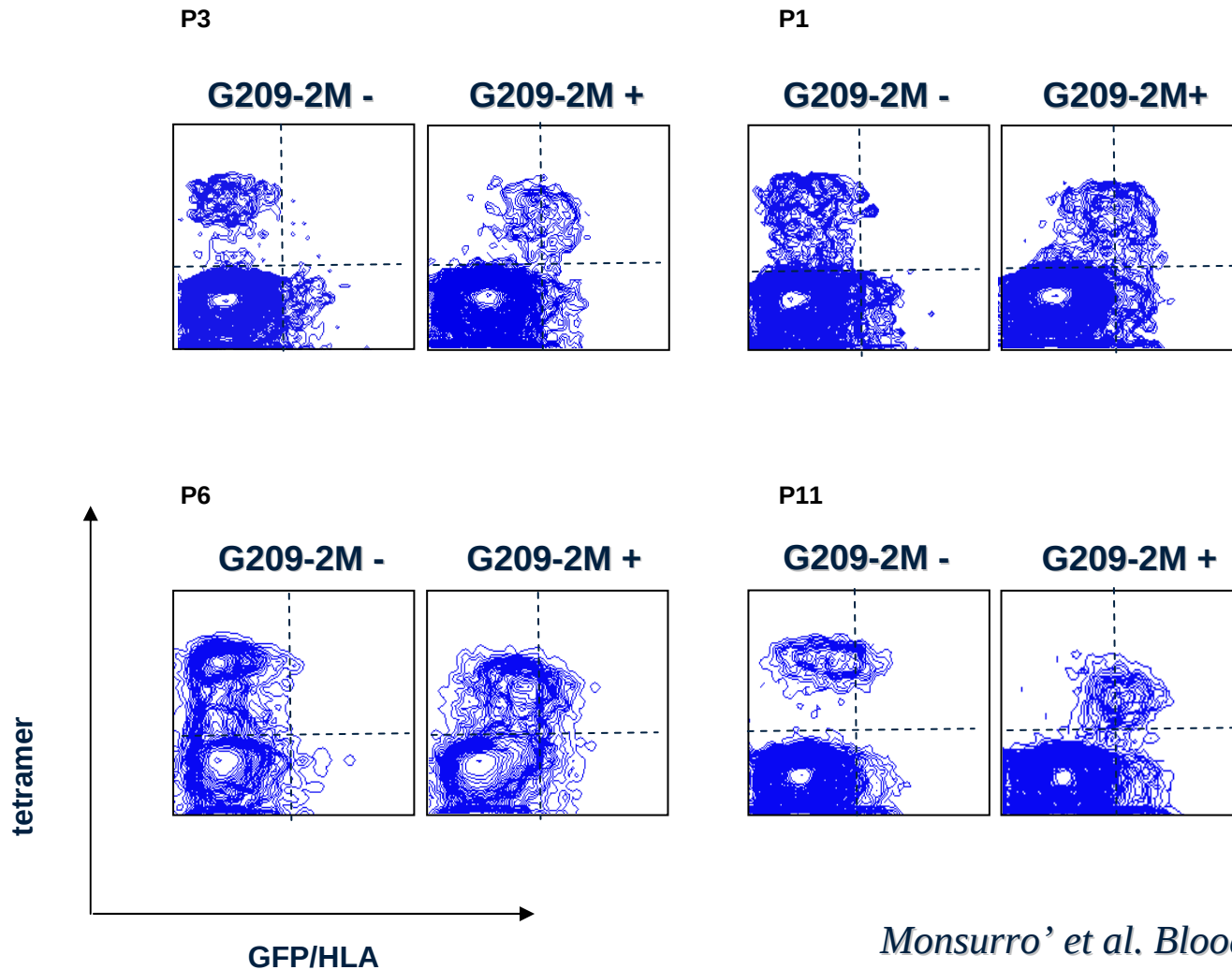


Ex vivo cytotoxicity of immunization-induced CD8+ T cells



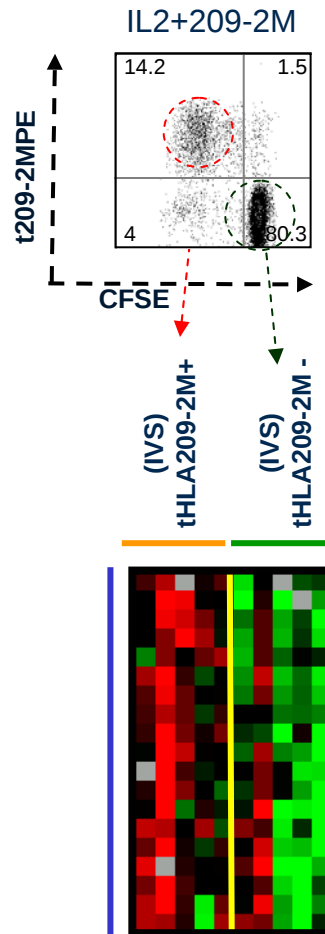
Monsurro' et al. Blood 2004

GFP-HLA fusion complex incorporation *ex vivo* by CD8+ immunization-induced T cells

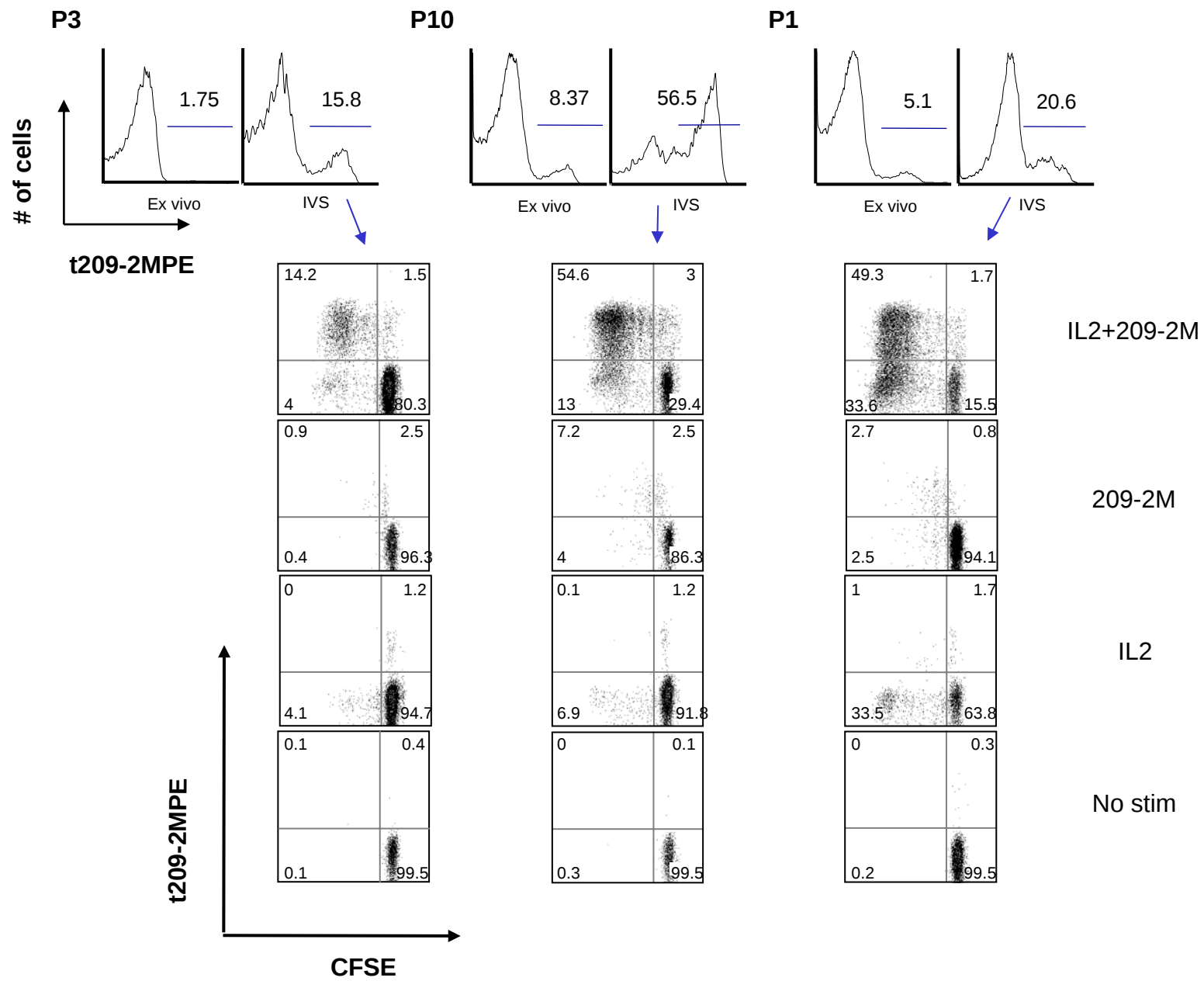


Monsurro' et al. Blood 2004

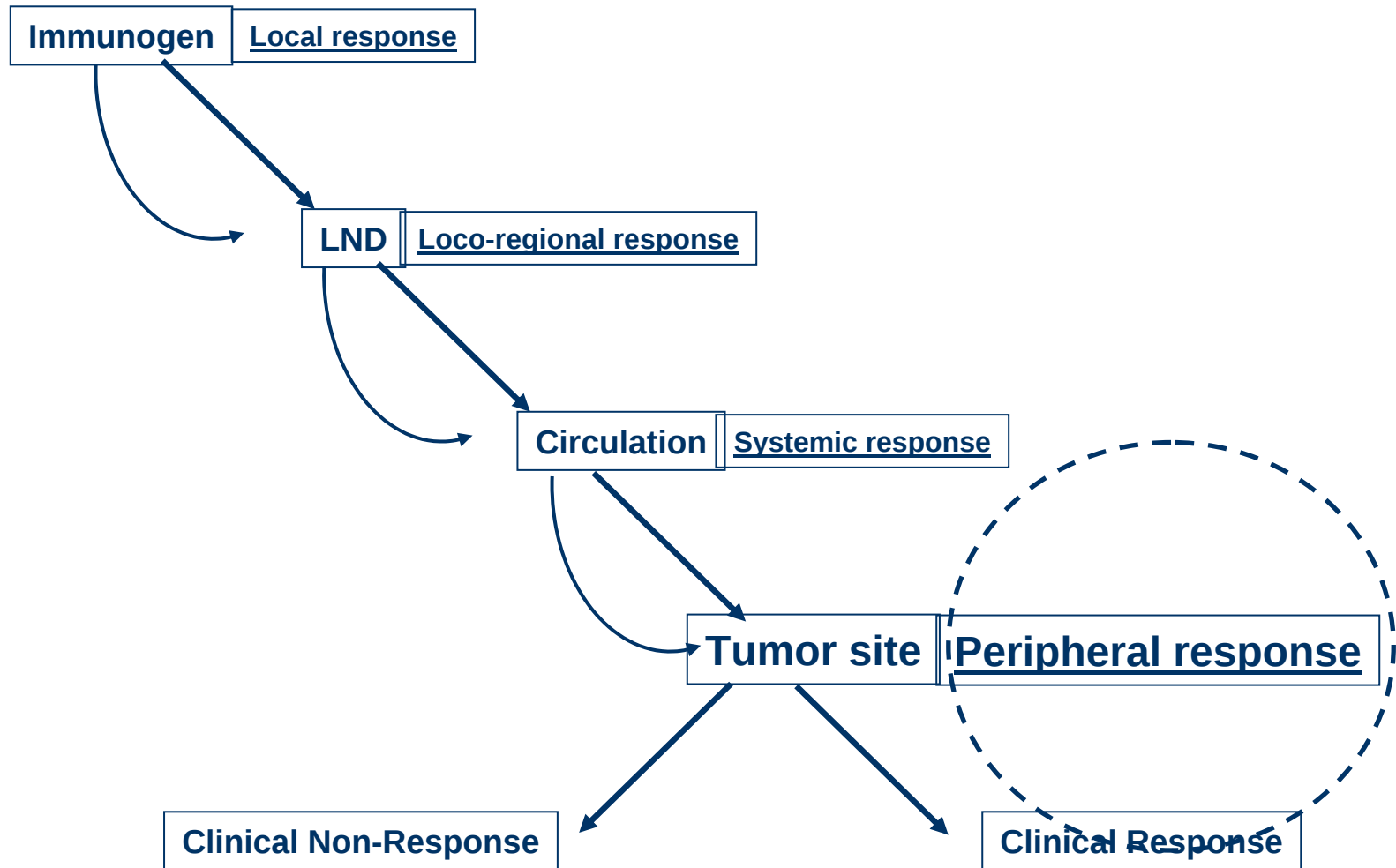
Preferential proliferation of Ag-specific T cell



EphB2 (ptk)
 Bak=bcl2 family
 Nitrogen activated PK3
 Cyclophilin B
 Annexin A8
 Cyclophilin A
 Nitrogen activated PKK3
 Mortality factor 4 like 2
 ISGF3 γ (IFN α/β responsive TF)
 Nitrogen activated PK3
 Eukariotic translation factor
 Cyclin D3
 NTF2
 MPK1
 Guanine nucleotide binding protein
 Lck
 Fibroblast growth factor 2
 Tubulin α 1
 PTP type 6



Global Approach: Biological Considerations



Marincola et al. Trends in Immunol. 2003

Studying the tumor micro-environment

Excisional Biopsies

- Good quantity of material to study
- Do not allow serial sampling of same lesion
- Do not allow prospective assessment of natural history of a given lesion

Fine Needle Aspirates

- Limited quantity of material to study
- They allow serial sampling of same lesion
- They allow prospective follow up of a given lesion

Wang and Marincola, Immunol Today 2000

Multidimensionality of tumor/host interactions in the context of T cell aimed immunization

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Kinetics of IFN- γ and gp-100 expression in melanoma metastases

Treatment: gp100 based vaccine

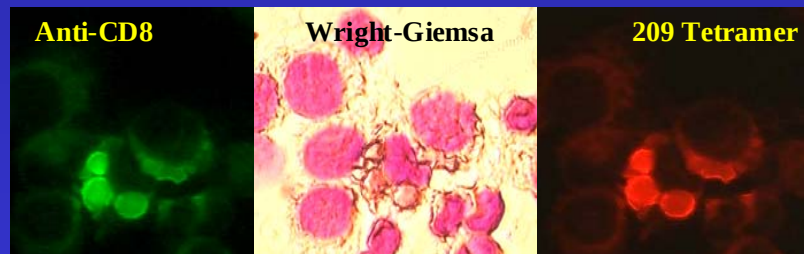
Question:

Vaccine-elicited T cell may not localize at tumor site.

Results:

Vaccine-elicited T cells

- 1) localize at tumor site
- 2) interact with the tumor cells
- 3) this is not sufficient for tumor rejection



Kammula et al., J. Immunol., 1999

Tumor Monitoring			
Site	IFN/CD8	Fold Inc	GP100/Actin
R axilla	568		1242
	<u>7586</u>	<u>13.4</u>	<u>1310</u>
L thigh	331		1956
	<u>11865</u>	<u>35.8</u>	<u>3955</u>
R axilla	1187		6186
	<u>7891</u>	<u>6.6</u>	<u>611</u>
L thigh	579		2865
	<u>7788</u>	<u>13.5</u>	<u>894</u>
R thigh	2231		1226
	<u>4452</u>	<u>2.0</u>	<u>235</u>
L chest	1013		1
	<u>5532</u>	<u>5.5</u>	<u>18</u>
L med knee	3247		0
	1649	0.5	<u>1</u>
L lat knee	2865		1
	2131	0.7	<u>1</u>
RL thigh	140		4786
	<u>1585</u>	<u>11.3</u>	<u>2291</u>
RU thigh	466		532
	759	1.6	<u>312</u>
R groin	692		60
	<u>1474</u>	<u>2.1</u>	<u>12</u>

Multidimensionality of tumor/host interactions in the context of T cell aimed immunization

Immunology



1st dimension = TCR/HLA/peptide interaction

2nd dimension = Importance of co-stimulation

3rd dimension = Localization at tumor site

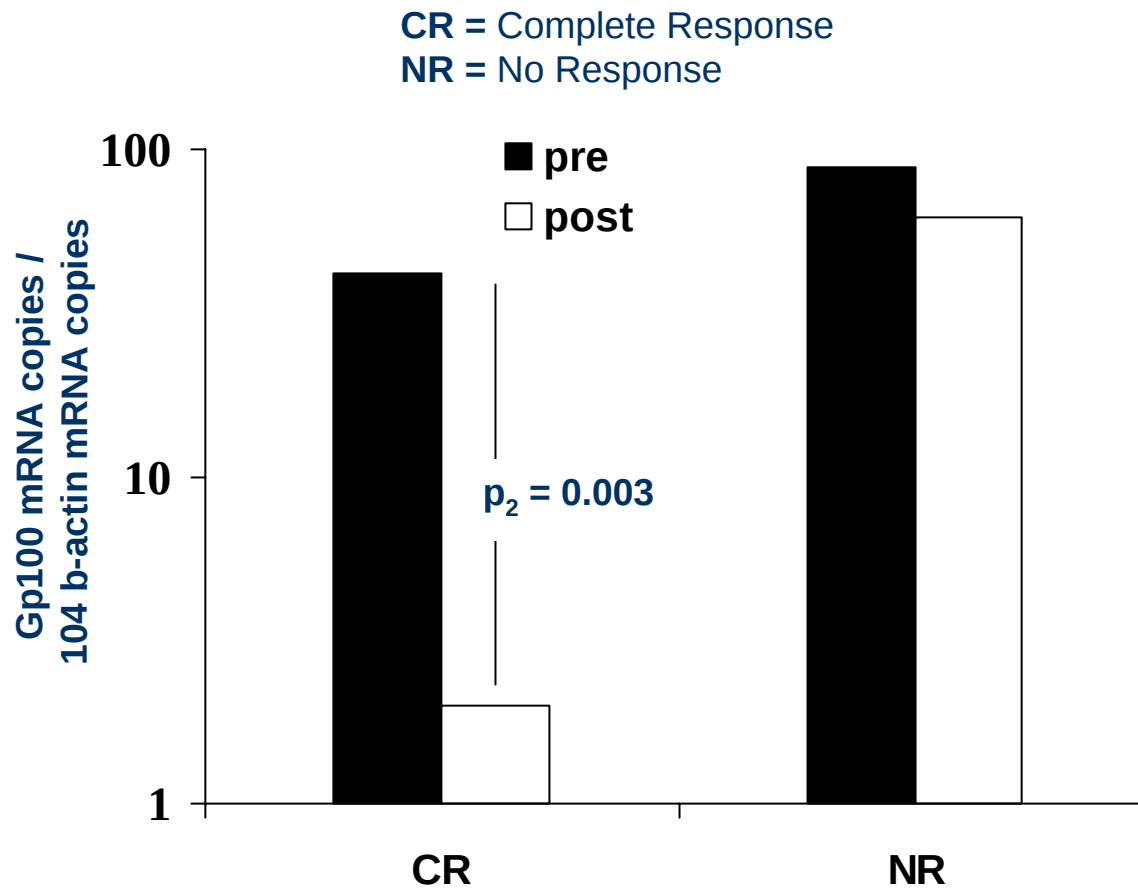
Tumor Biology



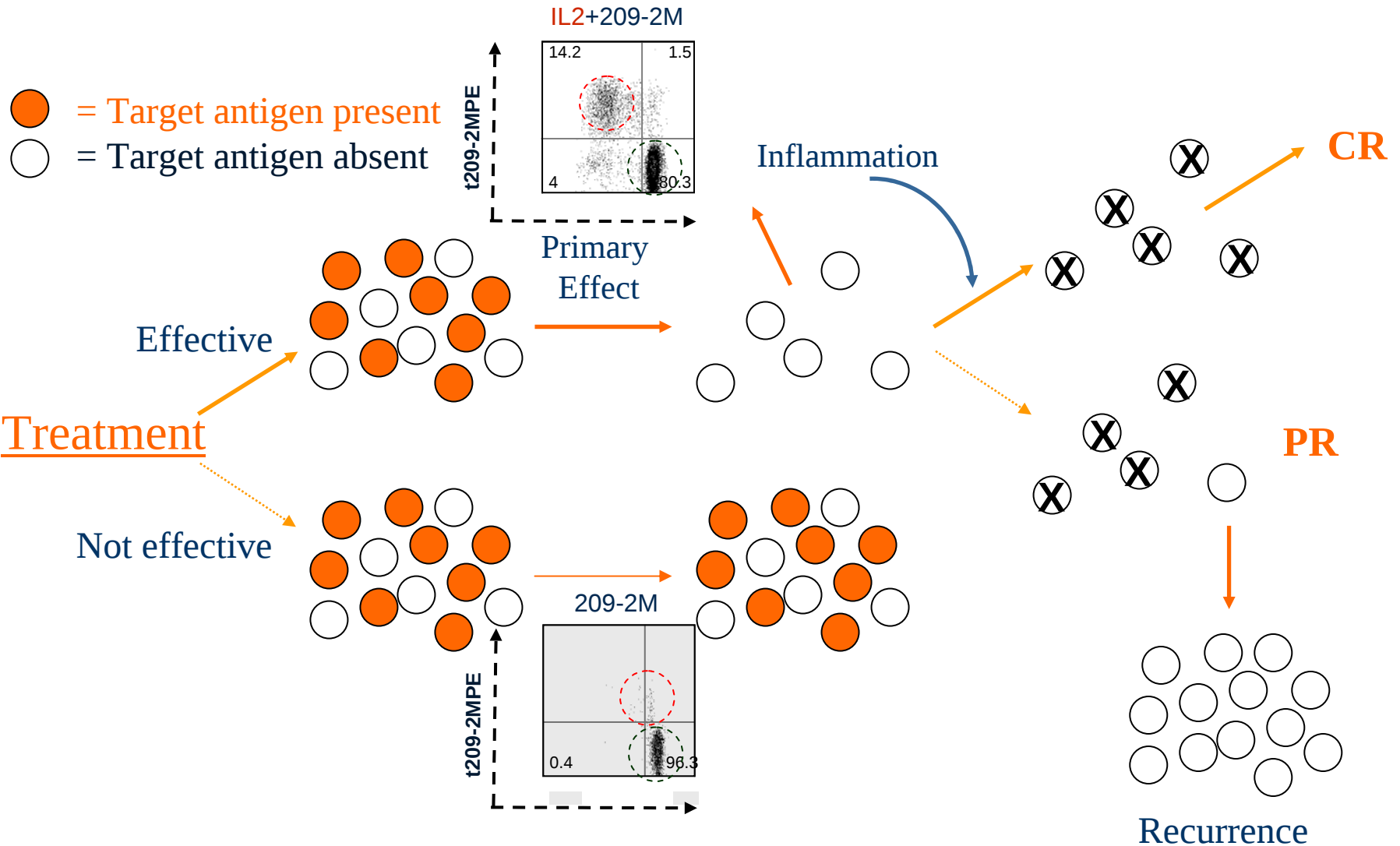
4th dimension = Evolving nature of immune response and
genetic instability of cancer cells

5th dimension = Heterogeneity of the tumor micro-environment

Tumor variability and evolving with time



Proposed hypothesis of how antigen-specific therapy might affect target antigen expression



Multidimensionality of tumor/host interactions in the context of T cell aimed immunization

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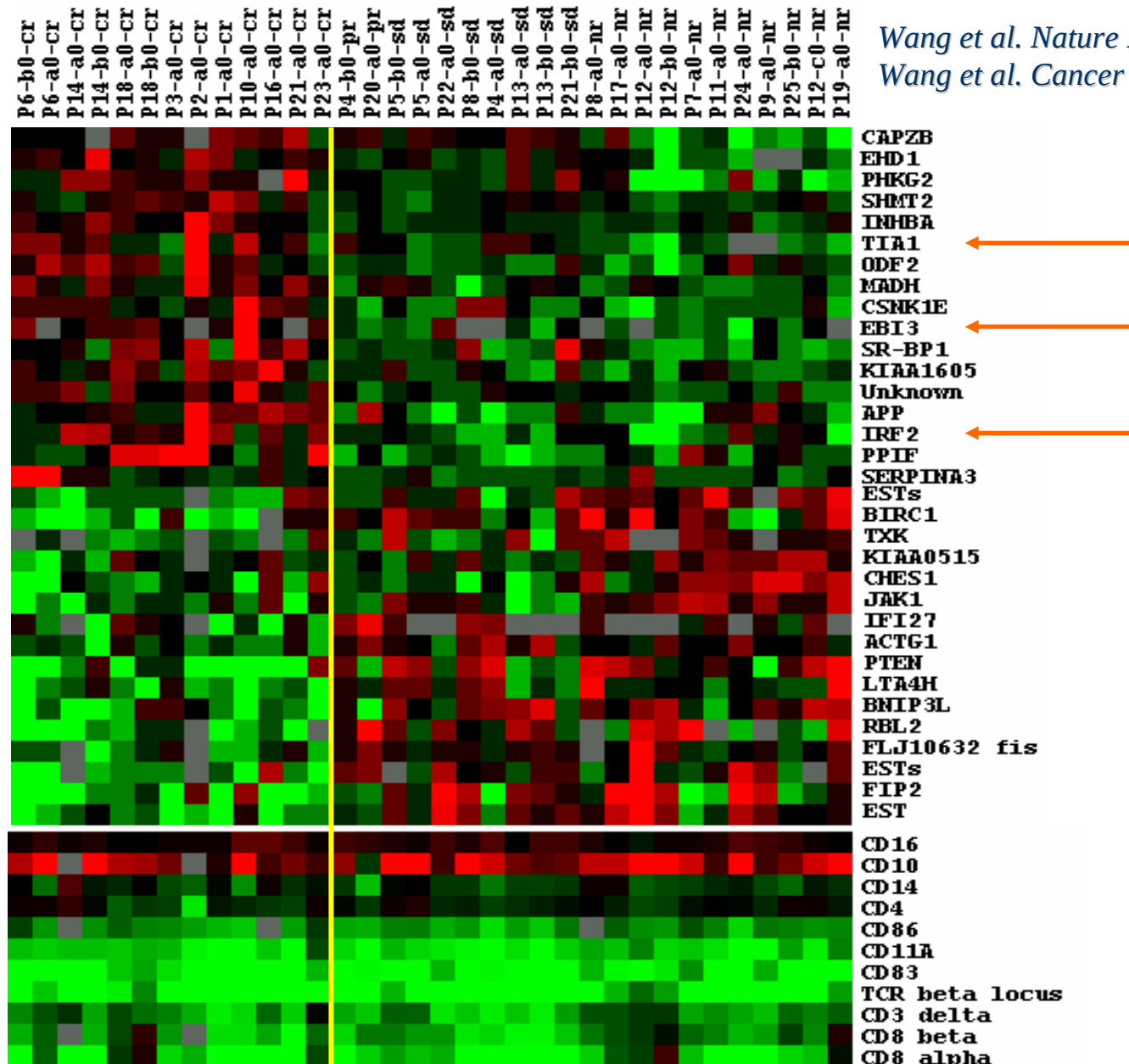
**4th dimension = Evolving nature of immune response and
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A global approach to Identify the algorithm responsible for tumor rejection in humans



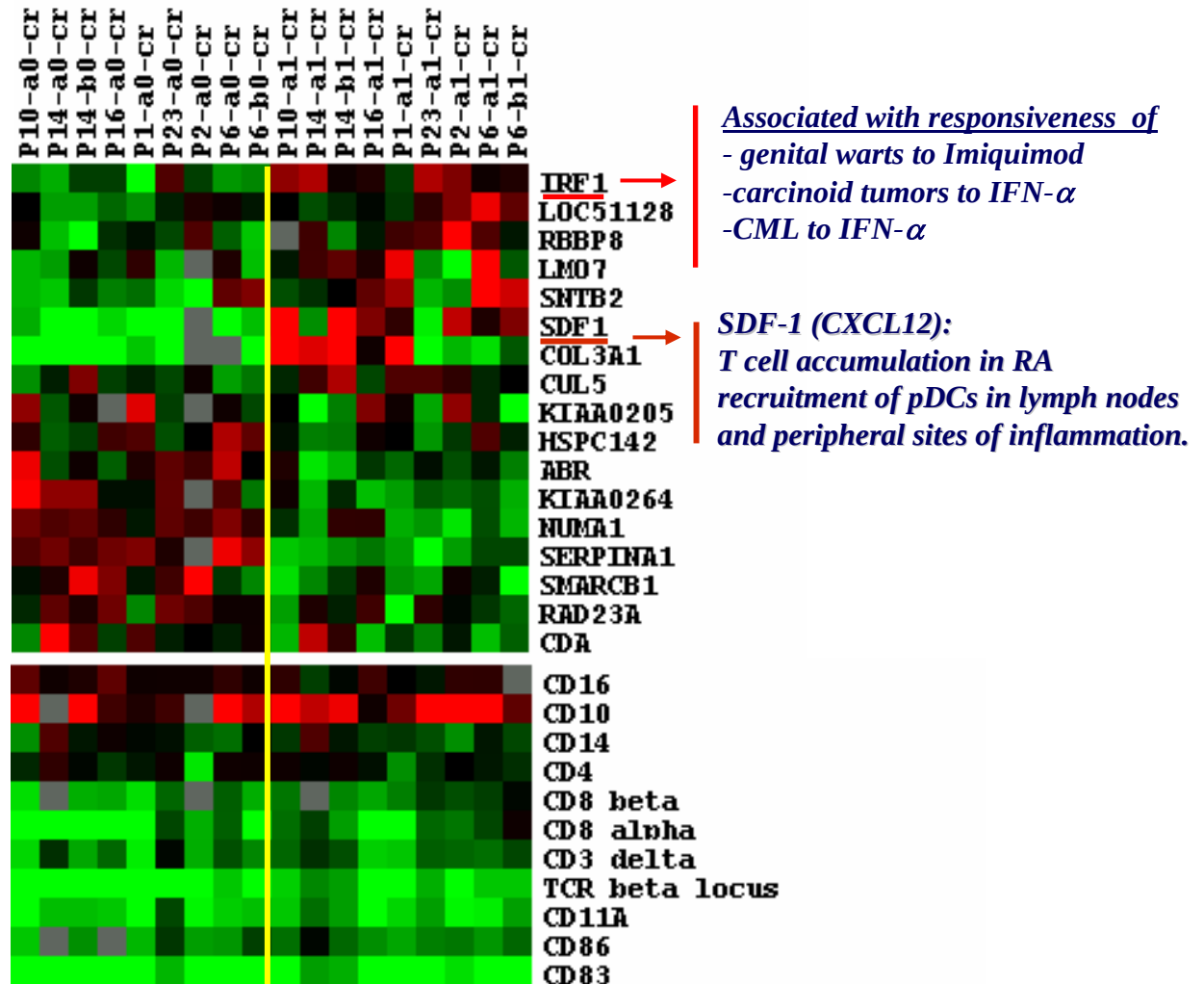
Genes differentially expressed pre-treatment in immune responsive metastases



Wang et al. Nature Biotech 2000

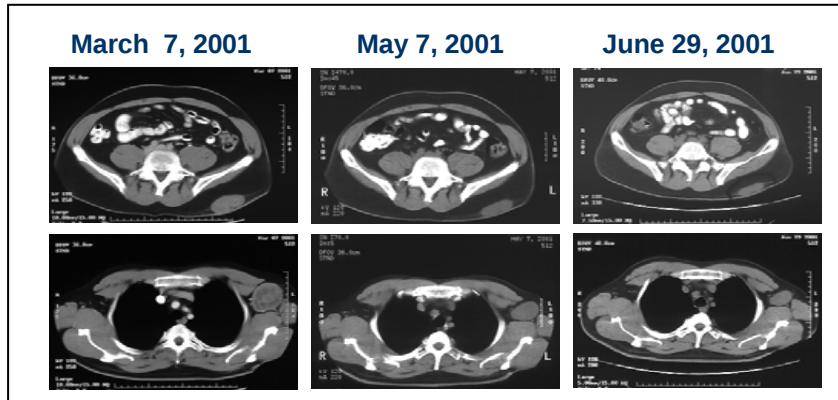
Wang et al. Cancer Res. 2002

Genes differentially expressed between pre- vs post-treatment CR

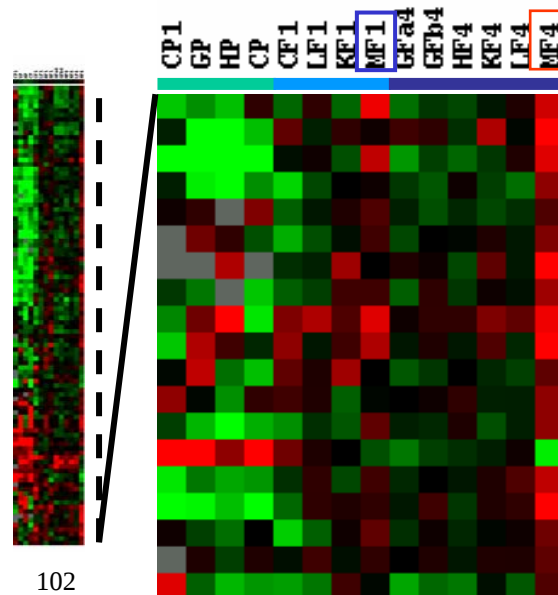


Genes associated with immune response during IL-2 therapy

Panelli et al Genome Biol 2002

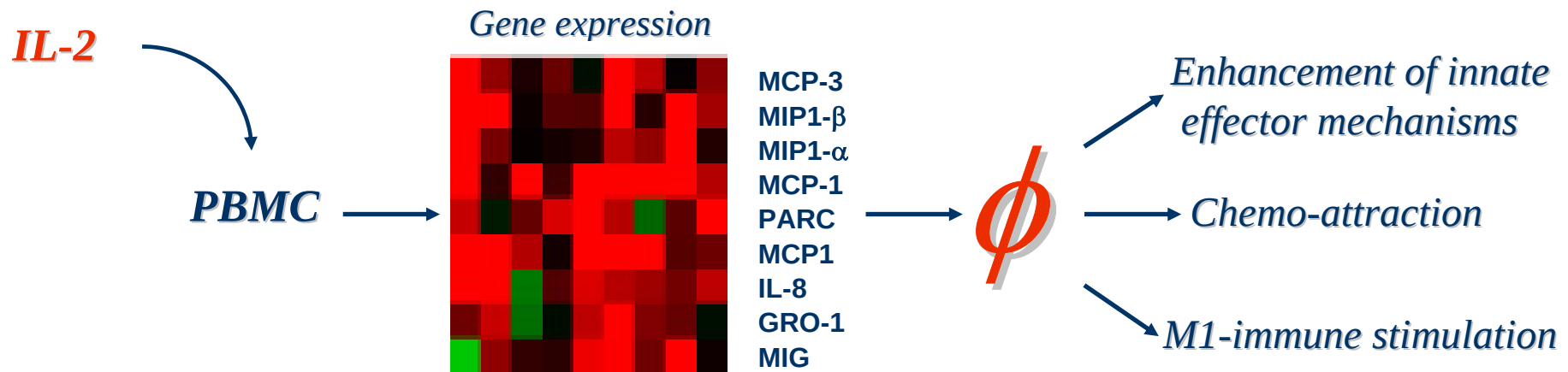


- CR LESSION POST IMMUNIZATION EXPRESSED GENE
- SIMILAR EXPRESSION TO NK EXPOSED TO II2
- UPREGULATED IN ACUTE REJECTION OF KIDNEY TRANSPLANT (PBMC AND RENAL BIOPSY TISSUE Sorwal, H. Immunol, 2001)

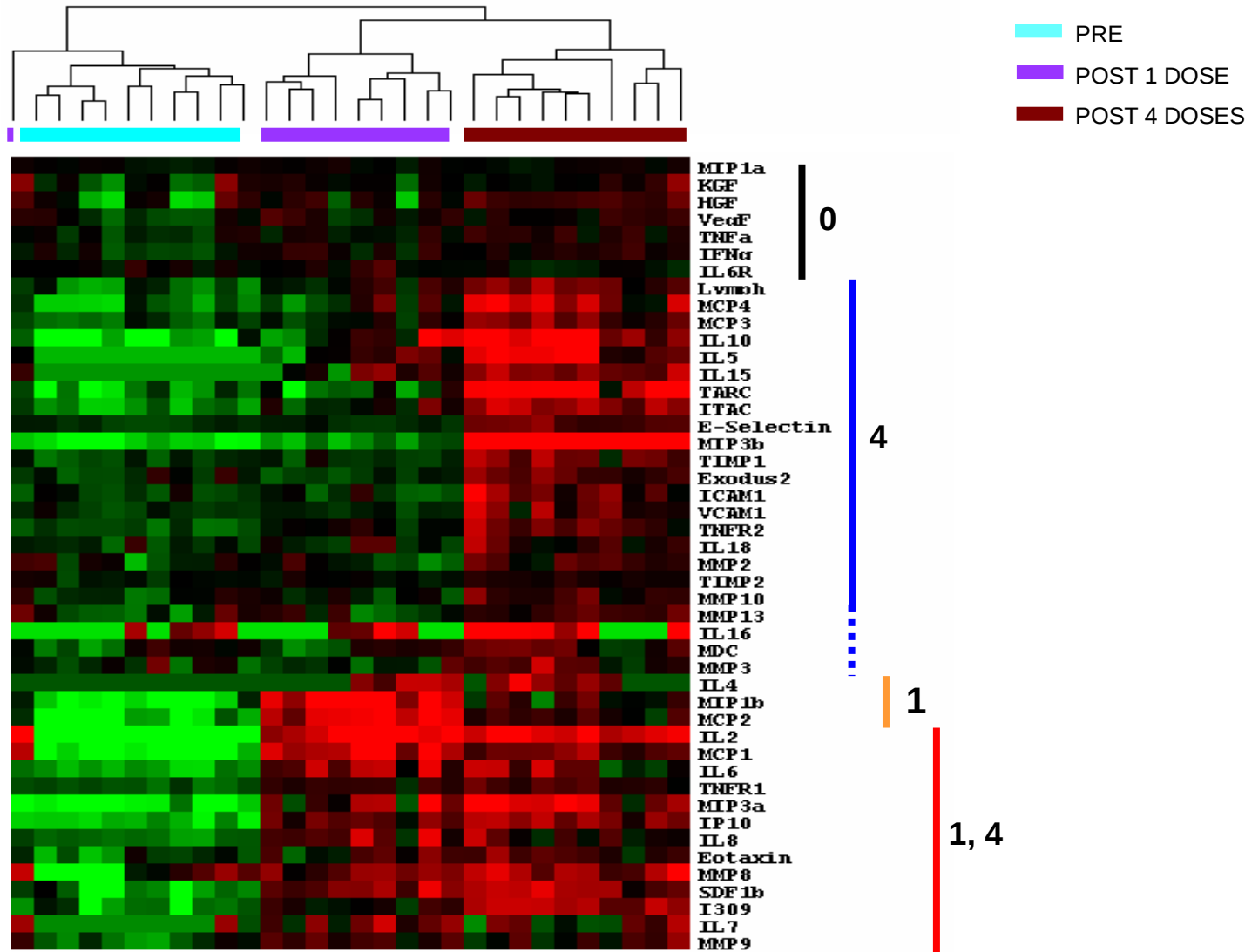


- TIA-1=nucleolysin cytotoxic granule ●
- NK4= natural killer cell protein 4 ●
- NKG5=granulysin ●
- EBI3 ●
- TCR alpha ●
- DAG kinase
- HLA class II region expressed gene KE4 ●
- MHC class II DR beta ●
- SERPINB1=Leukocyte elastase inhibitor
- MIP-1 delta
- FGF-13
- STIM1=Stromal interaction molecule 1
- VEGF
- CD62 P selectin ●
- GALECTIN 1 ●
- GALECTIN 1
- N-Myc
- DAP-1
- 53BP1=p53 binding protein

Postulated mechanism(s) of action of systemic IL-2 administration



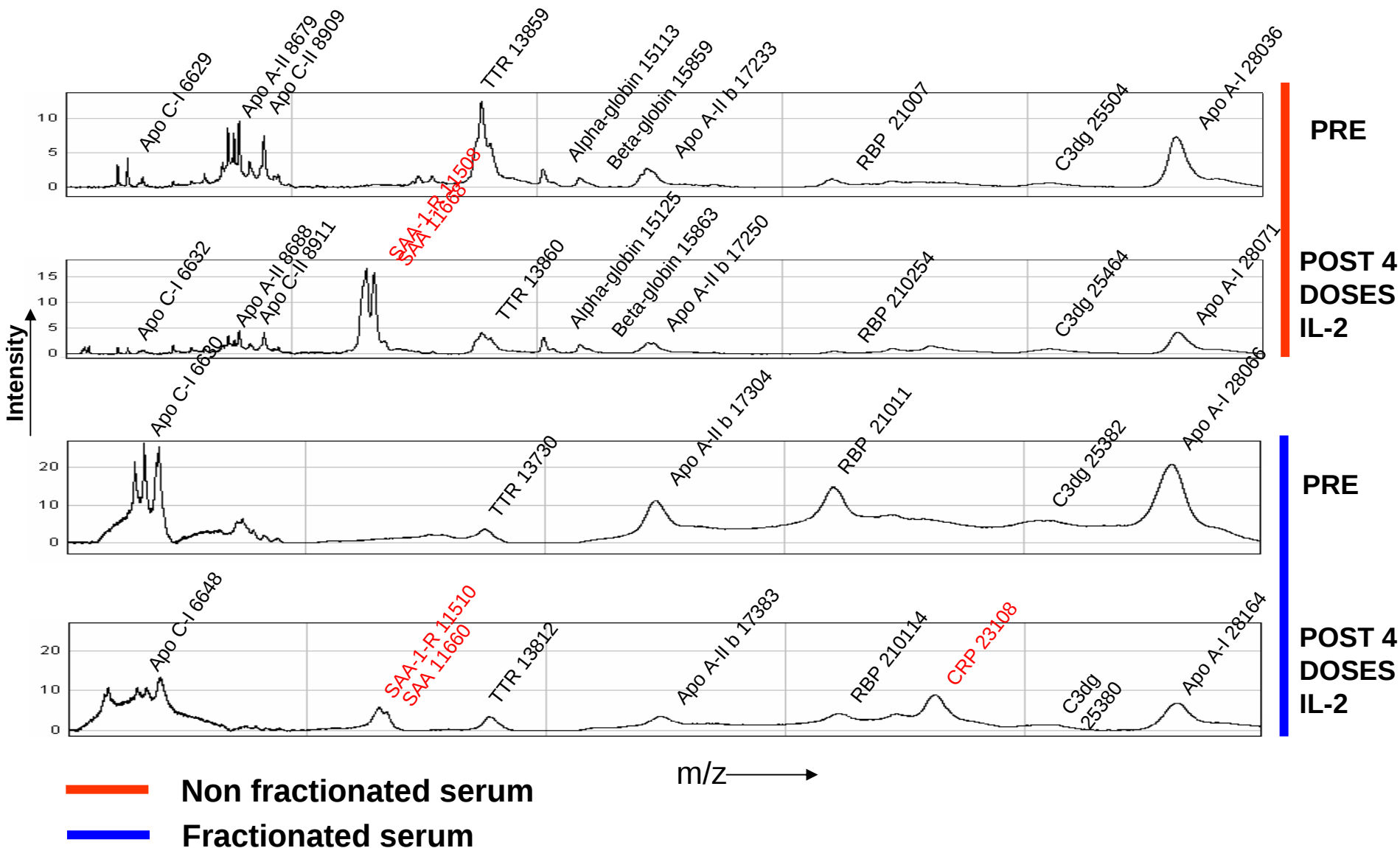
Unsupervised Hierarchical clustering of serum samples from RCC patients obtained pre. post 1 and post 4 doses of IL-2 (720.000IU/kg).



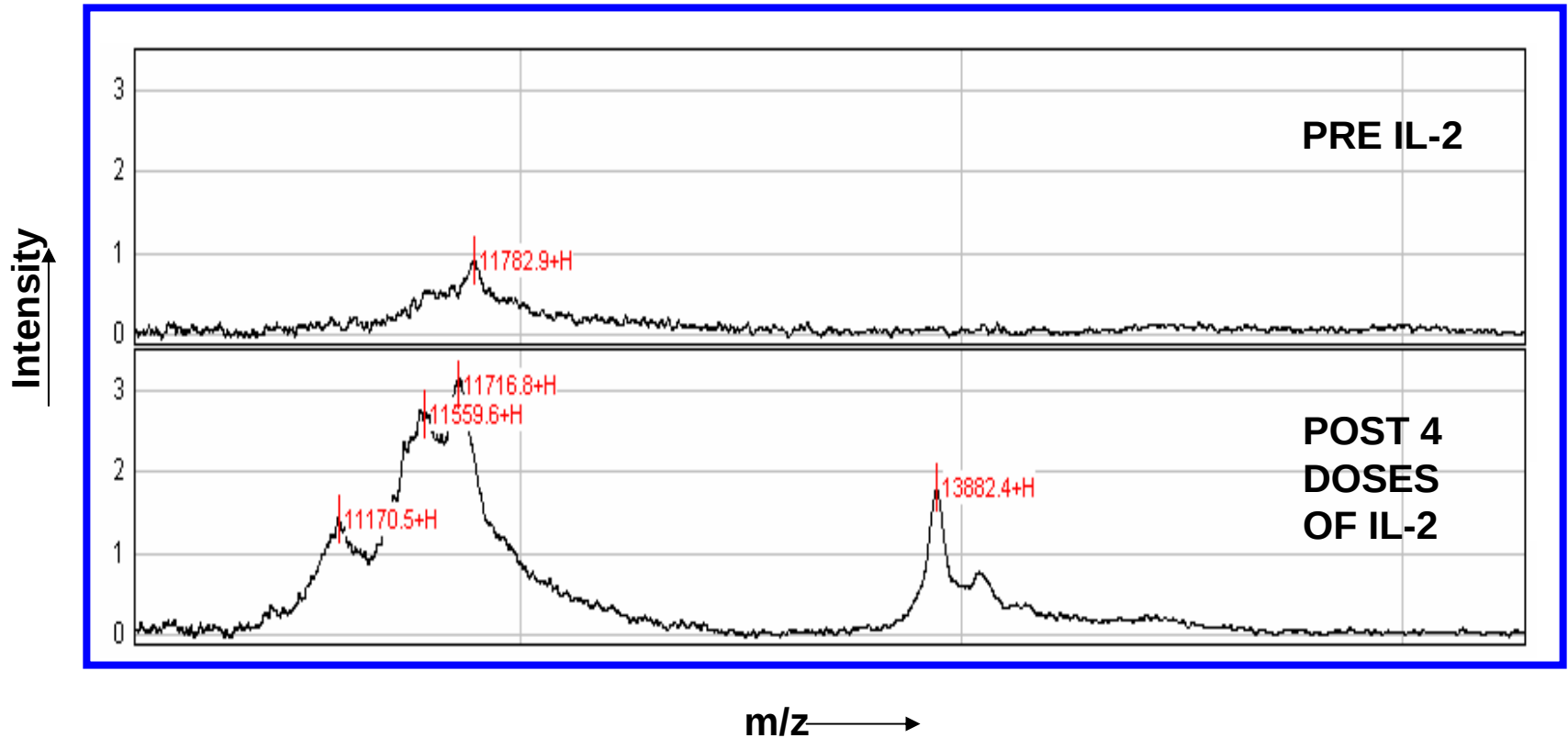
- =soluble factor minimally changing from pre to post 4 doses
- =soluble factor expression enhanced at 4 doses only
- = soluble factor expression enhanced post 1 dose
- = soluble factor expression enhanced at 1 and 4 doses

Panelli et al. J Translat Med, 2004

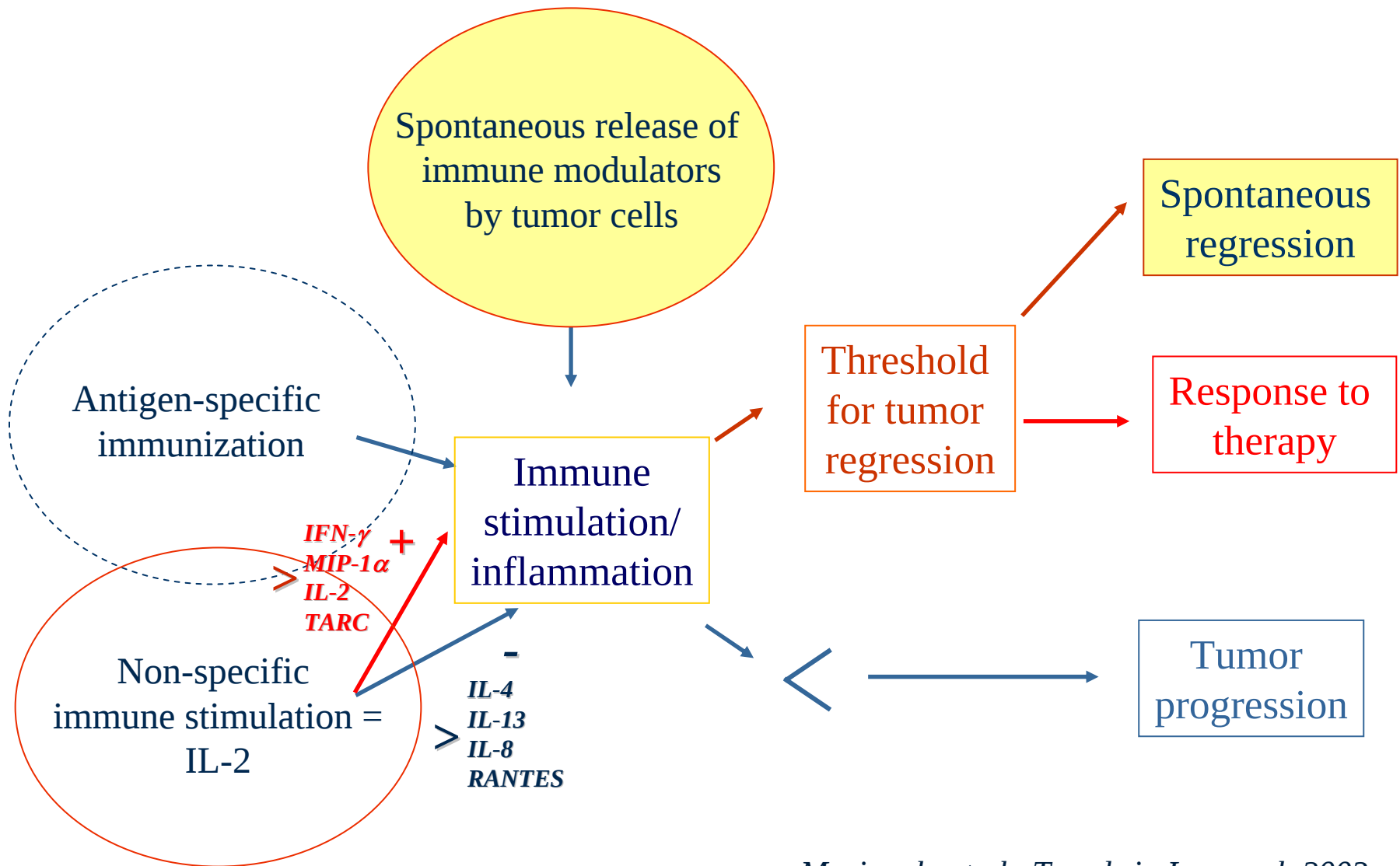
SAX2 SELDI ANALYSIS OF RCC serum



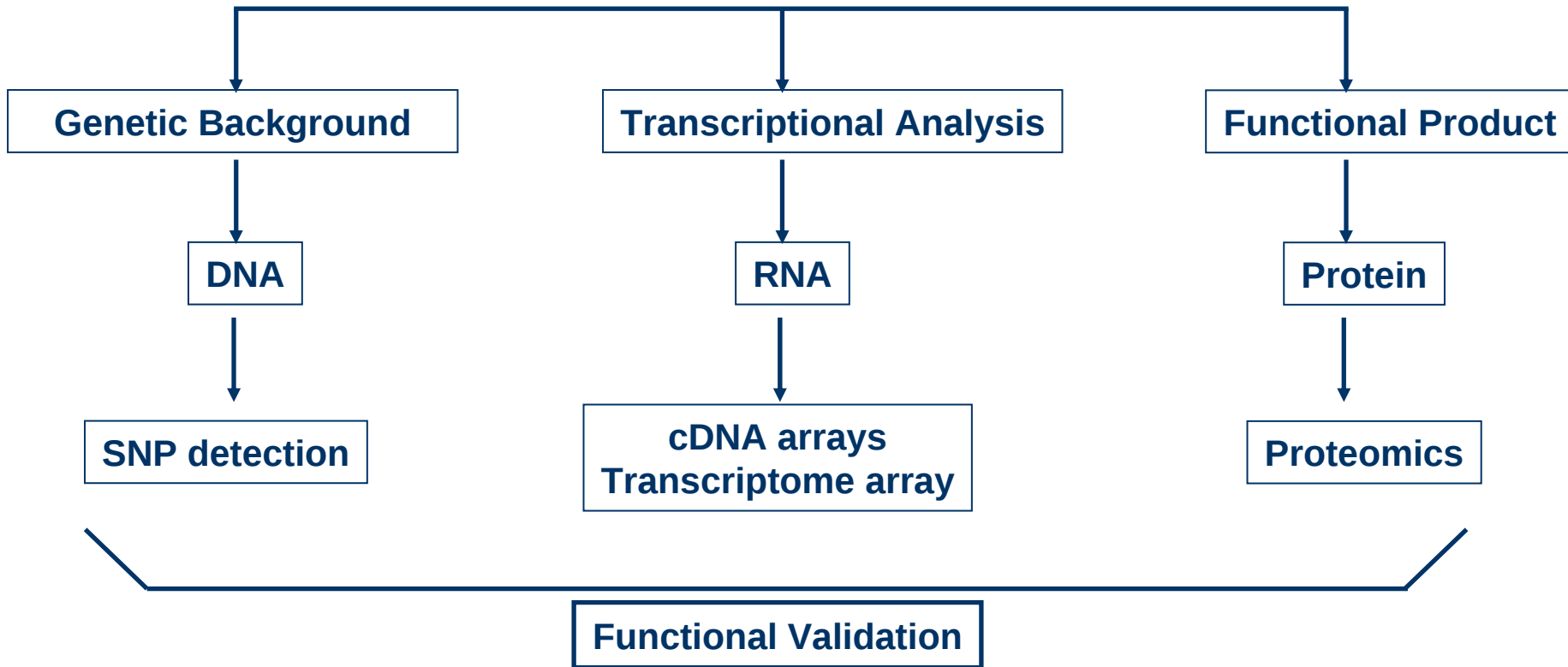
SELDI Immunoaffinity capture of SAA



Postulated algorithm of tumor immune responsiveness



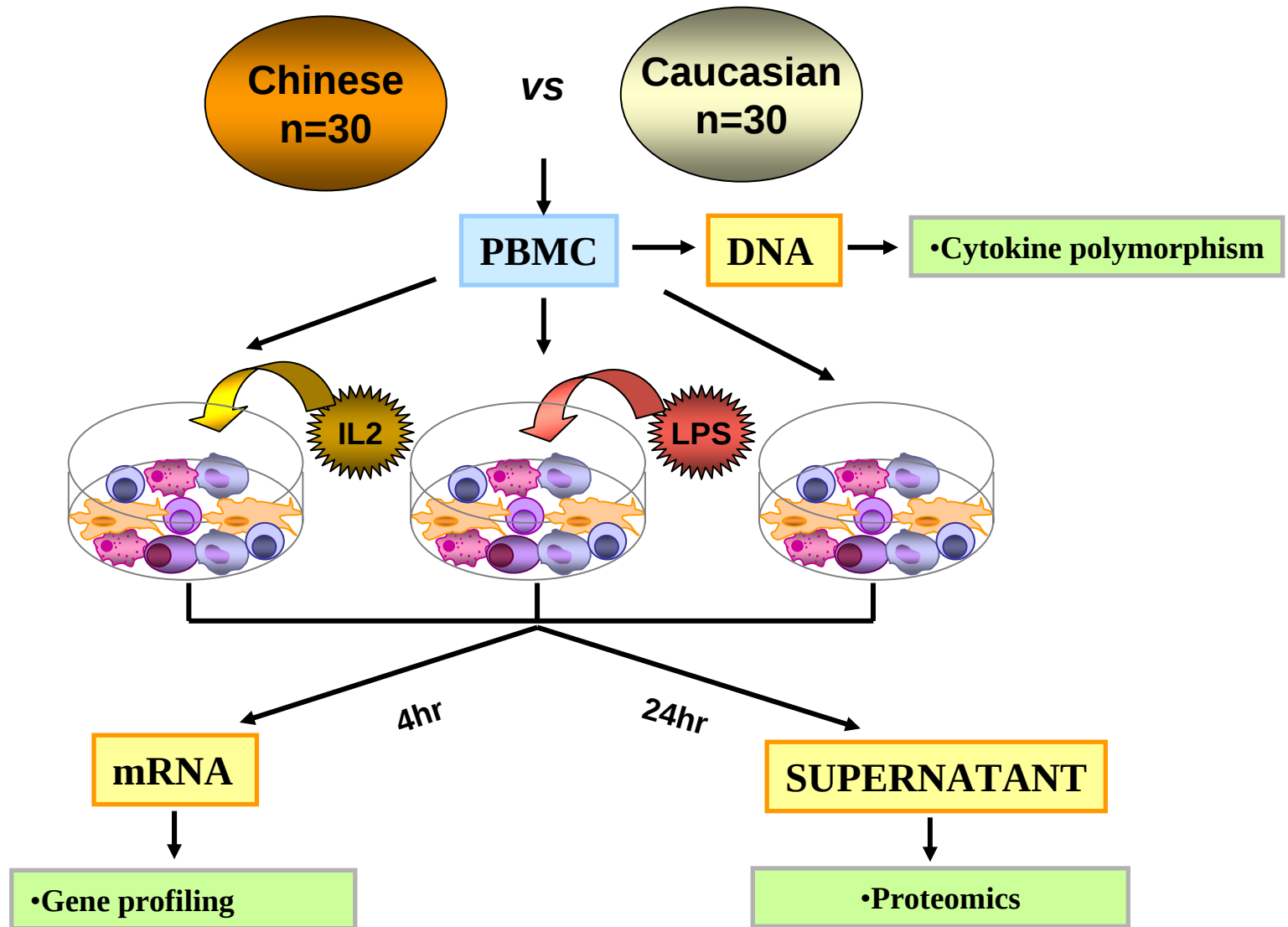
Global Approach: Technical Considerations



Hypothesis of the study:

Whether two prototype populations can be segregated according to functional and genetic parameters?

Functional and genetic differences between Chinese and Caucasian subjects in response to IL-2 or LPS



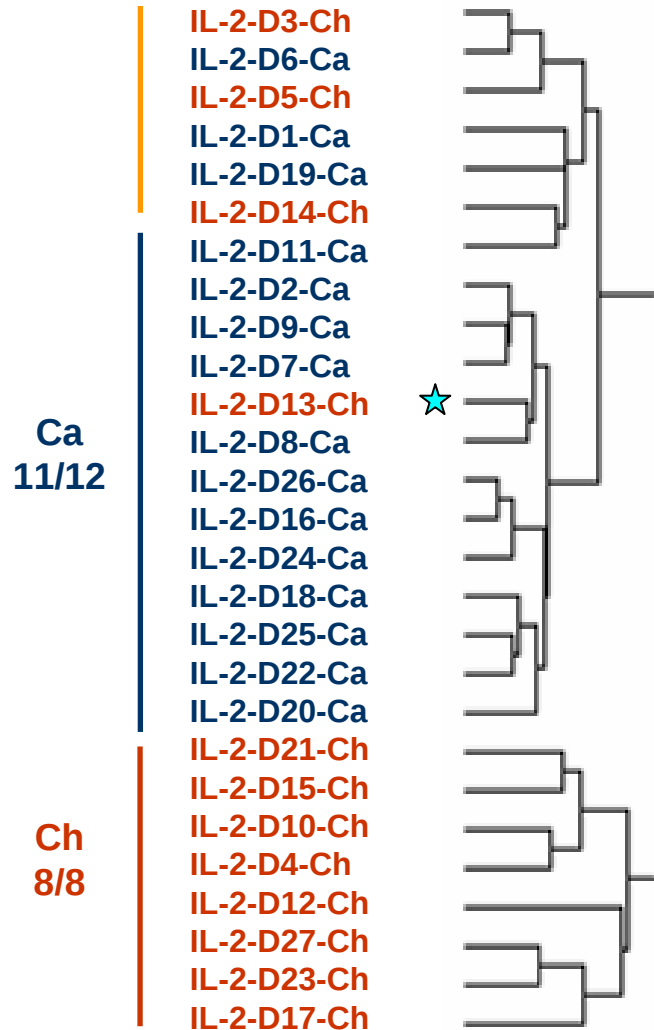
Identification of genes induced by IL2 or LPS in different ethnic groups

(Paired two sample t test, $p < 0.005$, exp present $> 80\%$, 16,000 total gene used)

	IL2 vs No-STI Caucasian N = 15	IL2 vs No-STI Chinese N = 12	LPS vs No-STI Caucasian N = 15	LPS vs No-STI Chinese N = 12
IL-2-induced genes (paired ($p < 0.005$))	808	209	989	344
Permutation	0.0017	0.06	0.0003	0.02

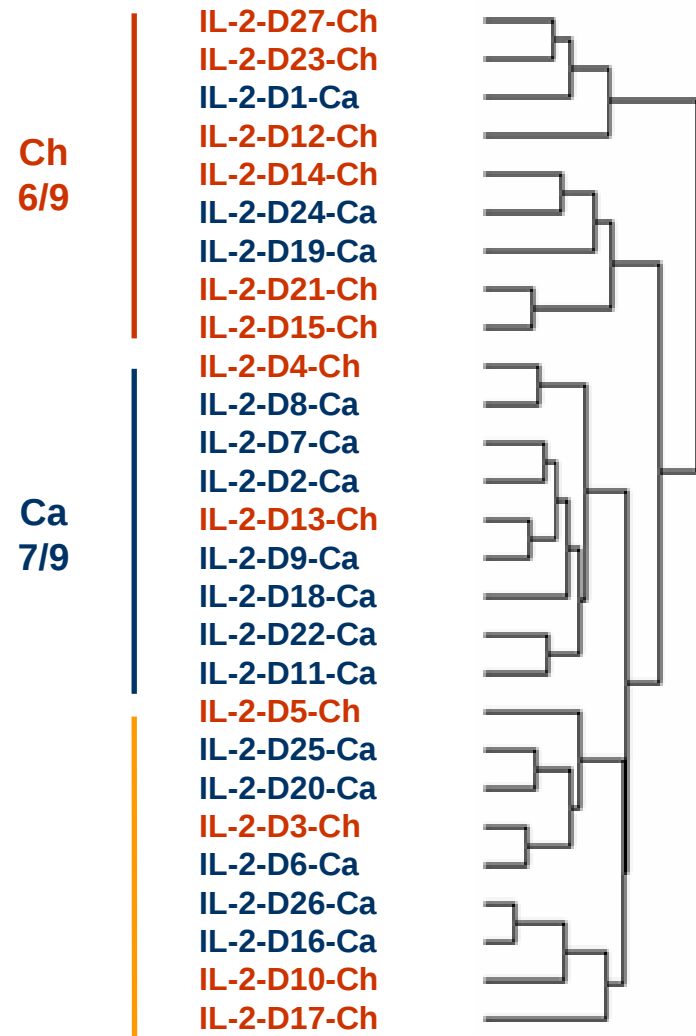
Ethnic Distribution based on IL2 inducible genes

Genes inducible in Caucasians 808 genes



Fisher test Ca vs Ch cluster; $p_2 < 0.001$

Genes inducible in Chinese 209 genes



Fisher test Ca vs Ch cluster; $p_2 = 0.15$

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Simone Mocellin
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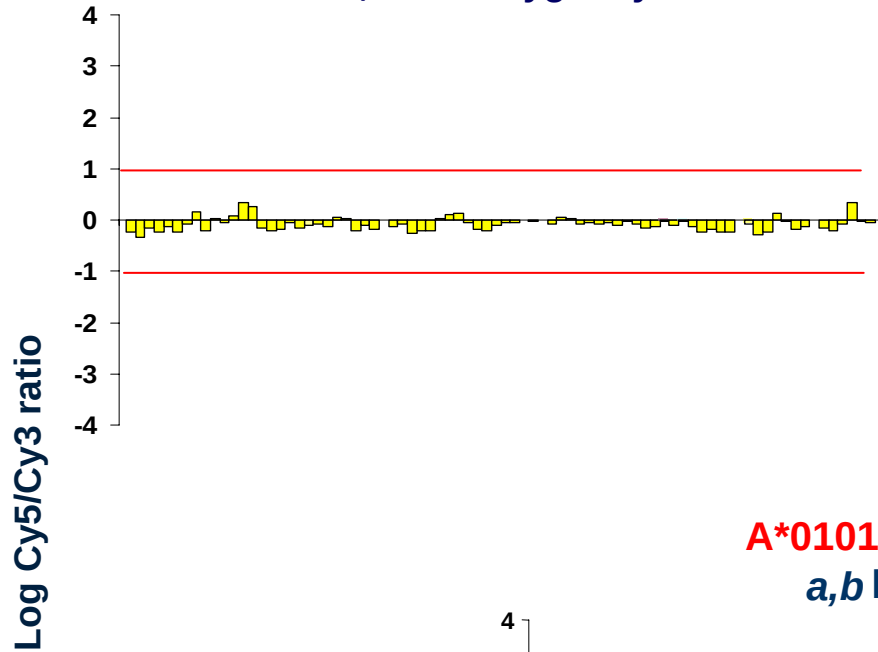
Collaborations

Meenhard Herlyn
Soldano Ferrone
Ralph Freedman
Jay Berzofsky
William Biddison
Ken Parker
David Garboczi
Lance Miller
Edison Liu
Jeffrey Trent
Polly Matzinger

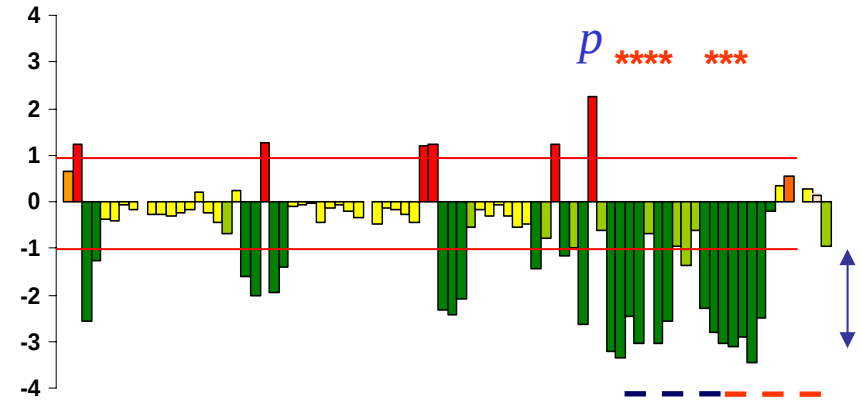


A new polymorphism-detection method for broad genome investigations in the context of clinical trials

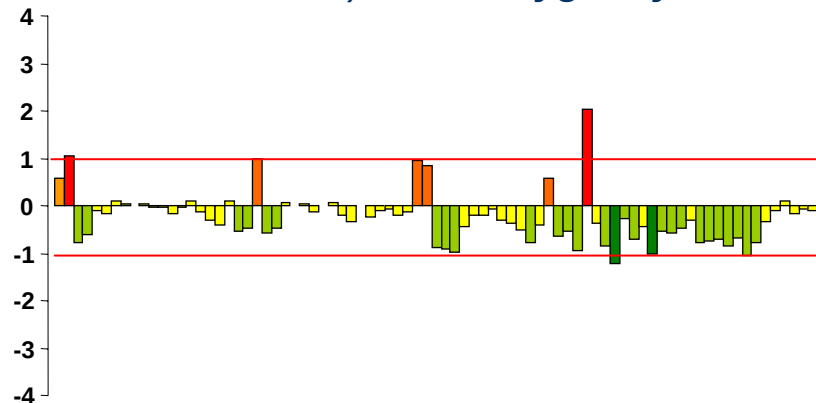
A*0101/A*0101
a,a homozygosity



A*0201/A*0101
b,b homozygosity

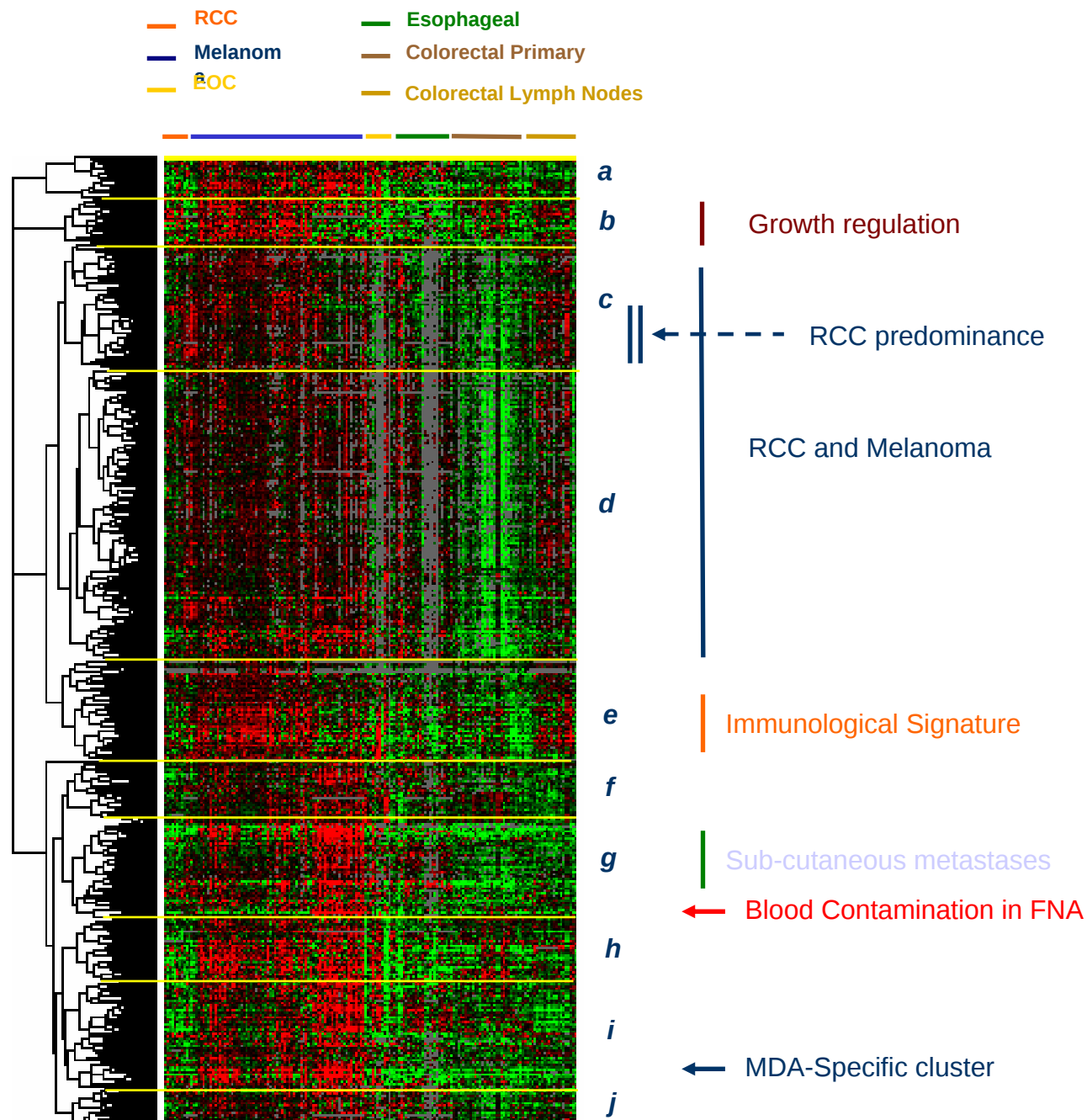


A*0101,0201 / A*0101
a,b heterozygosity



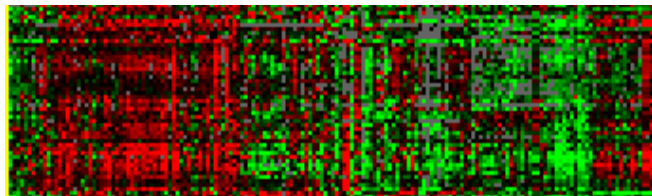
Special Thanks



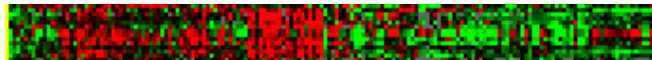


— RCC
— Melanoma
— EOC
— Esophageal
— Colorectal Primary
— Colorectal Lymph Nodes

— CM — LN - - - CM (FNA)



e



f-j

TGFBI4 || transforming growth factor beta 1 induced transcript 4 ||
 GZMA || granzyme A (granzyme 1, cytotoxic T-lymphocyte-associated
 TGFBRAP1 || transforming growth factor, beta receptor associated prote
 IL11RA || IL-11 receptor alpha chain ||
 TNFAIP2 || tumor necrosis factor, alpha-induced protein 2 ||
 FREB || Fc receptor homolog expressed in B cells ||
 || lymphocyte antigen 9 ||
 TNFRSF10B || tumor necrosis factor receptor superfamily, member 10b ||
 MARCO || MARCO=macrophage receptor with collagenous structure ||
 IFI16 || IFI16=interferon-gamma-inducible myeloid differentiation 1
 LEF1 || lymphoid enhancer-binding factor 1 ||
 CX3CR1 || CX3CR1=chemokine (C-X3-C) receptor 1=fractalkine receptor
 || interferon stimulated gene (20kD) ||
 IL-11R alfa || interleukin 11 receptor, alpha ||
 IL-21R1 || interleukin 21 receptor ||
 granzyme A || granzyme A (granzyme 1, cytotoxic T-lymphocyte-associated
 ICOS || inducible T-cell co-stimulator ||
	lymphocyte-specific protein tyrosine kinase	
	natural killer cell transcript 4	
	TNF receptor-associated factor 3	
TRADD		TNFRSF1A-associated via death domain
	interleukin 2 receptor, alpha	
	TNF receptor-associated factor 1	
	TNF receptor-associated factor 2	
IRF7		IRF-7=interferon regulatory factor-7
TNFRSF7		CD27
	lymphotoxin alpha (TNF superfamily, member 1)	
	lymphocyte-specific protein 1	
	chemokine (C-C motif) ligand 5	
CCL5		BLVS=BAFF=TALL-1=THANK=zTNF4=DTL=TNF family member that st
TNFSF13B		SLAMF1
ZAP70		zeta-chain (TCR) associated protein kinase 70kDa
GZMM		granzyme M (lymphocyte met-ase 1)
LY96		lymphocyte antigen 96
LY96		lymphocyte antigen 96
PTGIR		prostaglandin I2 (prostaglyclin) receptor (IP)
LILRB2		leukocyte immunoglobulin-like receptor, subfamily B (with
KLRK1		killer cell lectin-like receptor subfamily K, member 1
CX3CR1		chemokine (C-X3-C motif) receptor 1
	lymphotoxin beta (TNF superfamily, member 3)	
 IL-16 || interleukin 16 (lymphocyte chemoattractant factor) ||
 CD37 || CD37 antigen ||
 ITGAL || integrin, alpha L (antigen CD11A (p180), lymphocyte functi
 ITGAL || integrin, alpha L (antigen CD11A (p180), lymphocyte functi
 KLRG1 || killer cell lectin-like receptor subfamily G, member 1 ||
 IL17R || interleukin 17 receptor ||
 IL17R || interleukin 17 receptor ||
 ITGB7 || CD103 beta=Integrin beta 7 ||

RCC

Melanoma

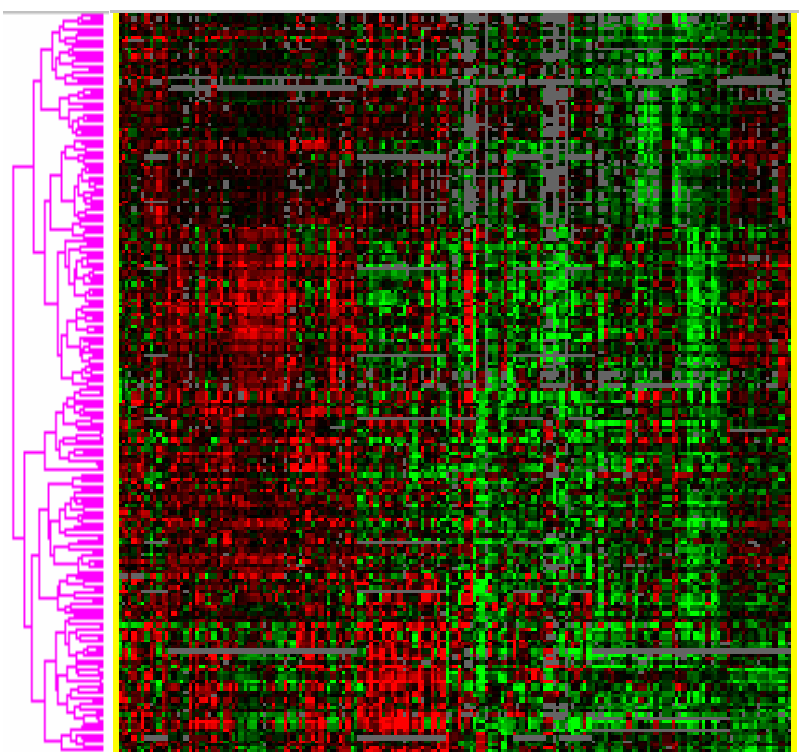
EOC

Esophageal

CRC Primary

CRC Lymph Nodes

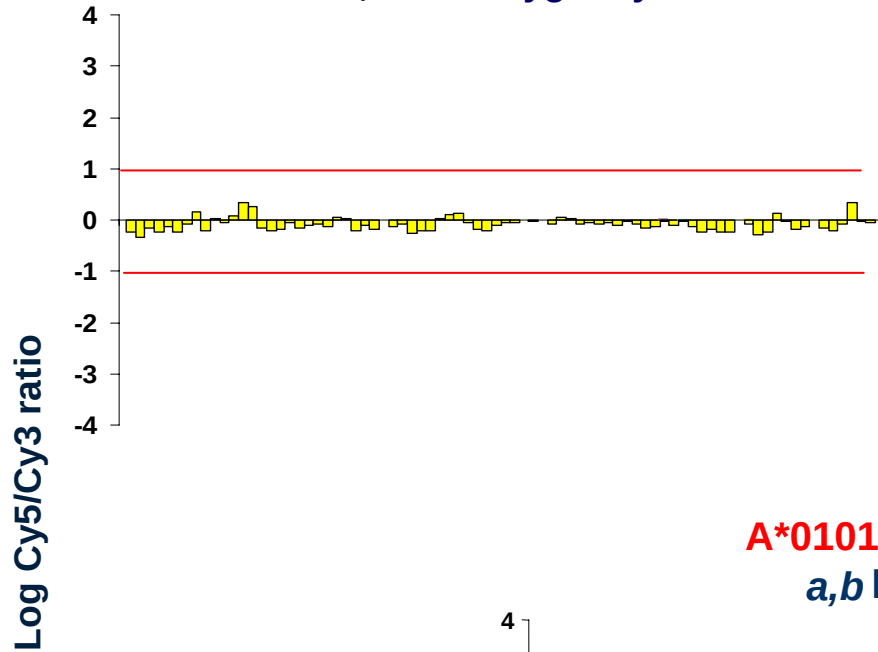
CM LN CM (FNA)



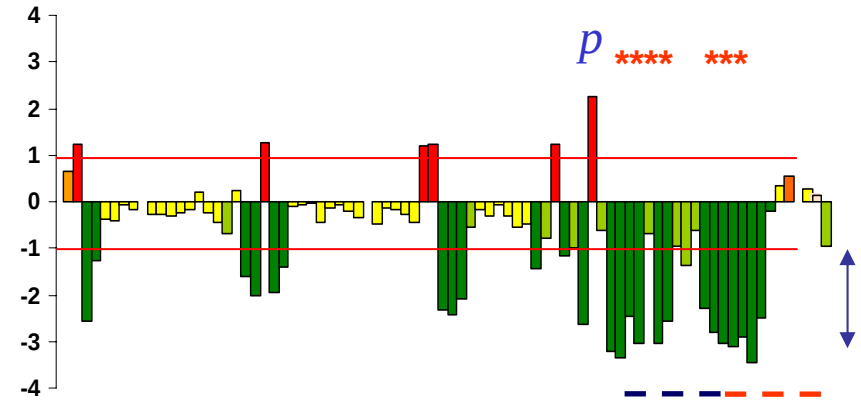
L1CAM || L1 cell adhesion molecule (hydrocephalus, stenosis of aqu
 IGFBP7 || insulin-like growth factor binding protein 7 ||
 ENO2 || ENO2=Enolase 2 (gamma, neuronal) ||
 ENO2 || enolase 2 (gamma, neuronal) ||
 CALU || calumenin ||
 MEF2C || MADS box transcription enhancer factor 2, polypeptide C (h
 PLOD || procollagen-lysine, 2-oxoglutarate 5-dioxygenase (lysine
 PTPRM || R-PTP-mu=protein tyrosine phosphatase, receptor type, M |
 PTPRM || protein tyrosine phosphatase, receptor type, M ||
 SPIRE1 || spire homolog 1 (Drosophila) ||
 CBL || c-cbl=Casitas B-lineage lymphoma protein=syk-inhibiting a
 MCAM || melanoma cell adhesion molecule ||
 MIF || macrophage migration inhibitory factor (glycosylation-inh
 HBXIP || hepatitis B virus x interacting protein ||
 HBXIP || hepatitis B virus x interacting protein ||
 SLC25A4 || solute carrier family 25 (mitochondrial carrier; adenine
 IKBKAP || inhibitor of kappa light polypeptide gene enhancer in B-c
 GPR56 || G protein-coupled receptor 56 ||
 CPEB4 || cytoplasmic polyadenylation element binding protein 4 ||
 CPEB4 || cytoplasmic polyadenylation element binding protein 4 ||
 RRAGD || Ras-related GTP binding D ||
 TBX2 || T-box 2 ||
 TBX2 || T-box 2 ||
 ADAMTS5 || a disintegrin-like and metalloprotease (reprolysin type)
 IMAGE34514 || SVAP1 protein ||
 SLC7A2 || solute carrier family 7 (cationic amino acid transporter,
 MITF || microphthalmia-associated transcription factor ||
 MITF || microphthalmia-associated transcription factor ||
 SLC16A4 || solute carrier family 16 (monocarboxylic acid transporter;
 SDCCAG8 || serologically defined colon cancer antigen 8 ||
 LAMA1 || laminin, alpha 1 ||
 SMA5 || SMA5 ||
 FUT11 || fucosyltransferase 11 (alpha (1,3) fucosyltransferase) ||
 SDC3 || syndecan 3 (N-syndecan) ||
 APOE || apolipoprotein E ||
 TMEM22 || transmembrane protein 22 ||

A new polymorphism-detection method for broad genome investigations in the context of clinical trials

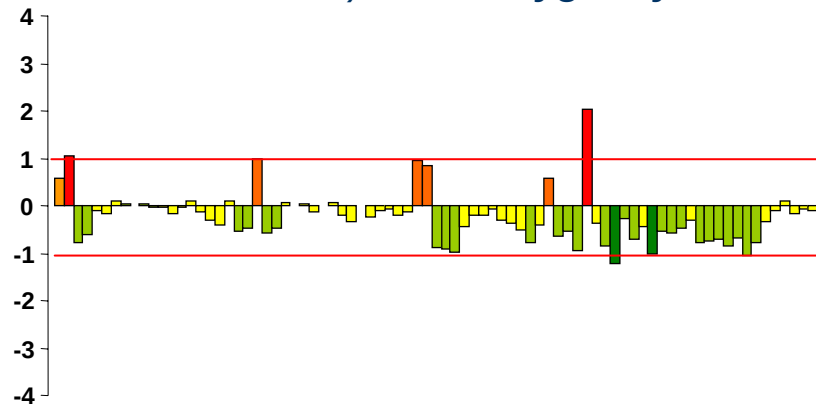
A*0101/A*0101
a,a homozygosity



A*0201/A*0101
b,b homozygosity



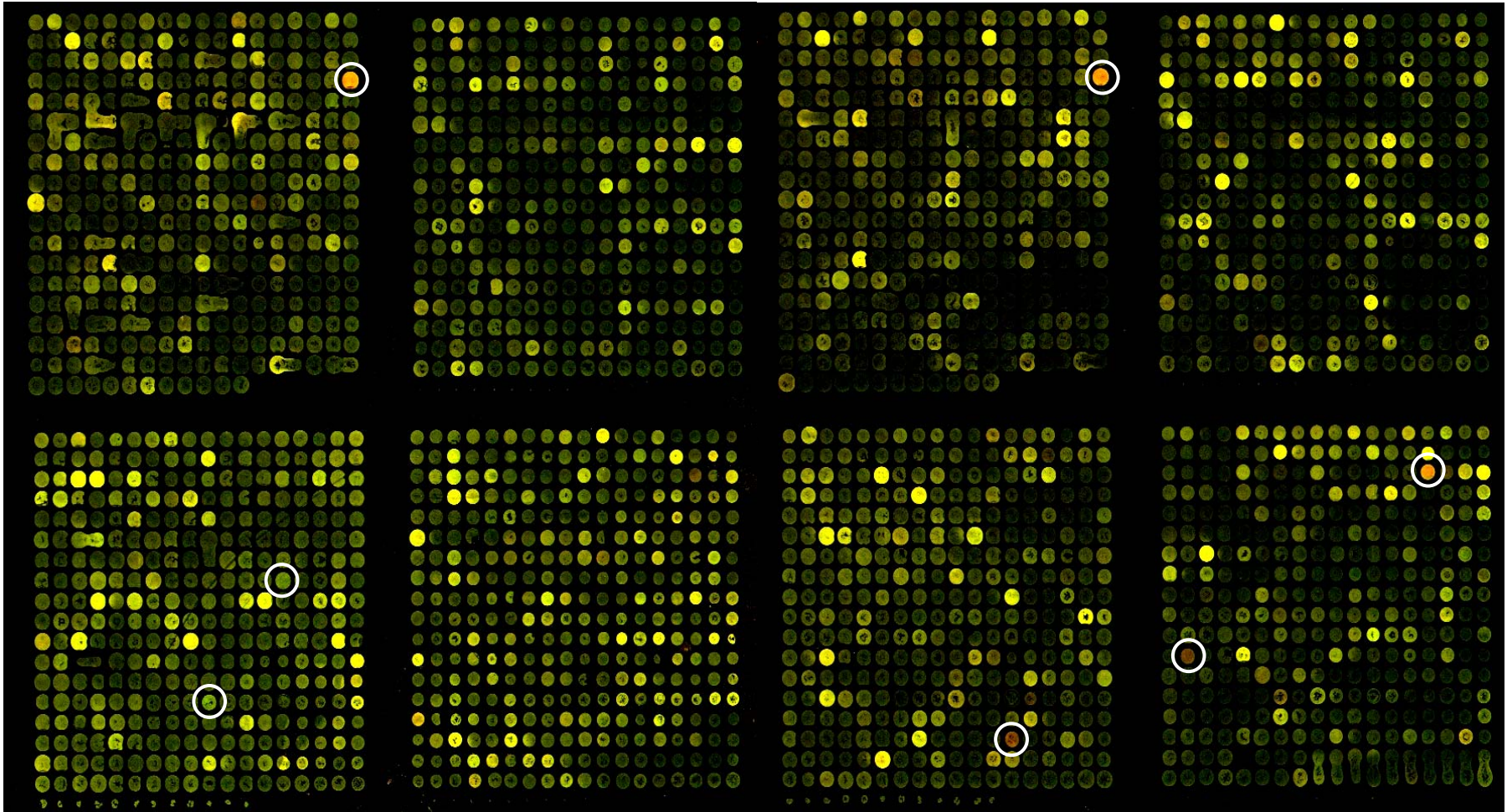
A*0101,0201 / A*0101
a,b heterozygosity



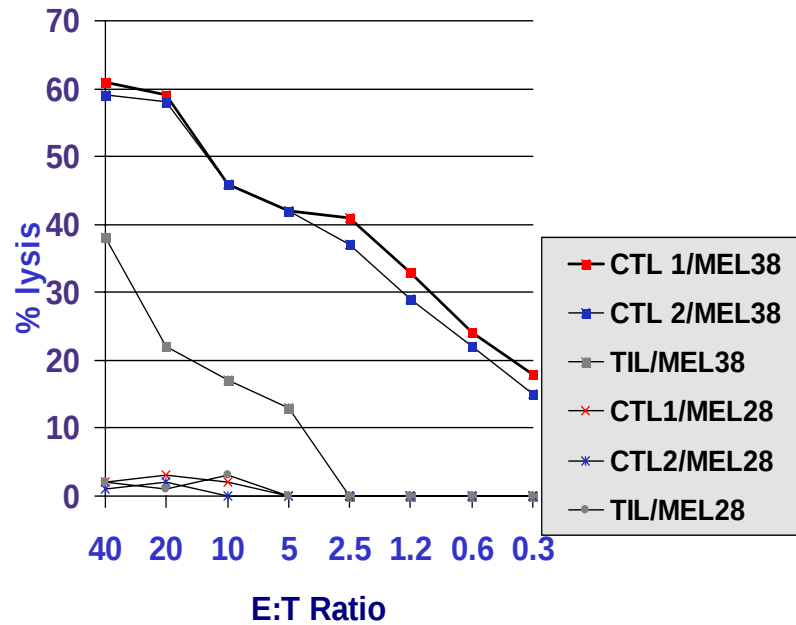
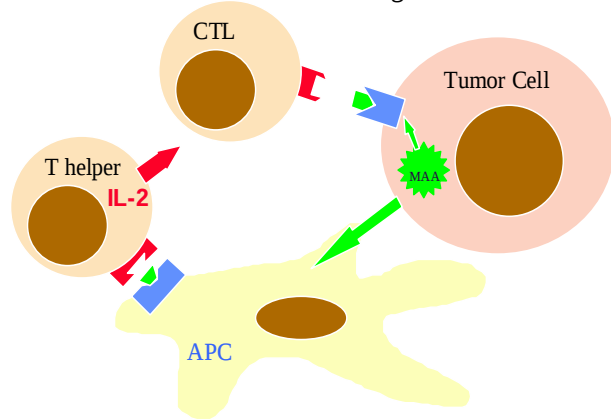
Analysis of the effect of human polymorphism on immune responses:
Cytokine polymorphism chip

Gene family Name	Gene number	Oligo number
TGF	7	202
IFN	21	490
CSF	5	156
TNF	48	1520
IL	80	3501
IRF	8	516
STAT	9	296
JAK	21	1208
NF-kB	21	1332
TLR	10	630
NK cell	25	544
Total	255	10395

Cytokine polymorphism detection chip

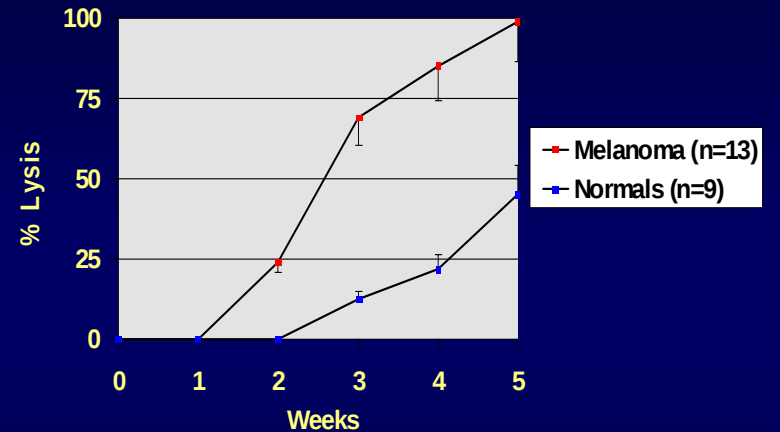
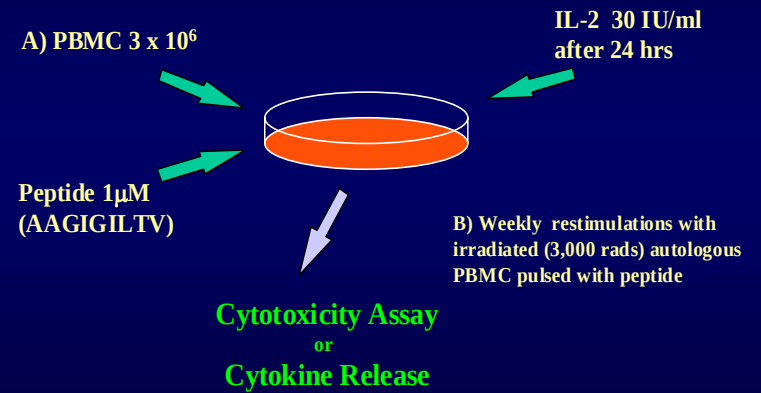


MHC Restricted T Cell Recognition of Tumor Cells



Rivoltini et al., J Immunol 1995

In Vitro Induction of Epitope Specific anti-Melanoma CTL



Differential anti-MART-1 Reactivity in the Peripheral Blood of Melanoma Patients in Comparison to Healthy Donors

Marincola et al., J. Immunother 1996

Conclusions

- **Comprehensive monitoring of cancer vaccines should be broadened from the study of systemic immune responses to include the evaluation:**
 - The immune responses at tumor site**
 - The genetic make up of each patient**
 - The genetic heterogeneity of individual patients' cancers at the transcriptional and the protein level**
- **Tools are now available that could be applied in the context of immunotherapy trials at relatively low cost and effort if samples are appropriately collected**

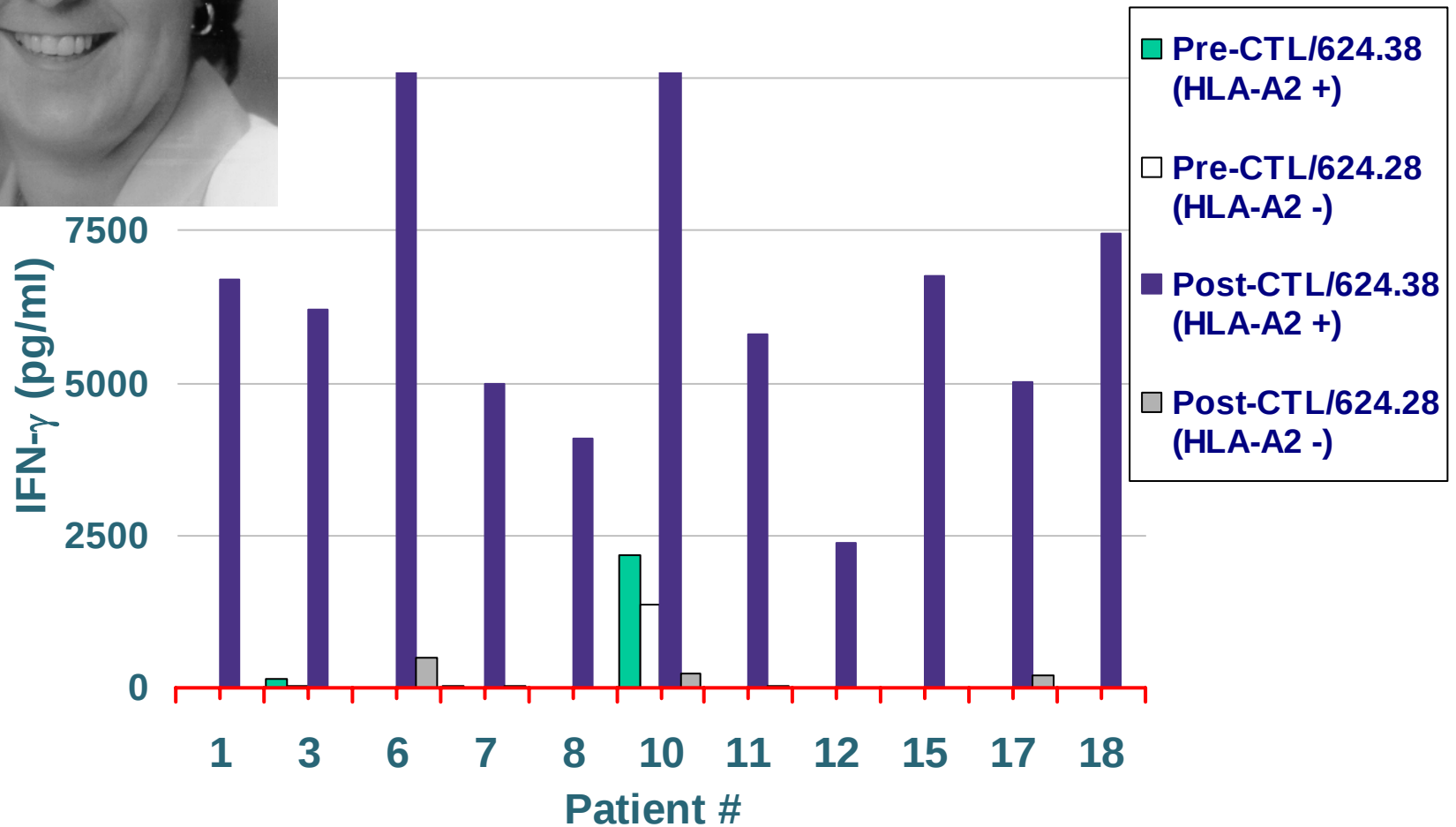
MAA of the melanocytic lineage (Melanoma Differentiation Antigens)

(expressed by 70 to 80 % of melanoma lesions)

MART-1 (118 aa)	27-35	HLA-A*0201	<u>AAGIGILTV</u>
	32-40	HLA-A*0201	ILTVILGVL
gp100 (661 aa)	154-162	HLA-A*0201	KTWGQYWQV
	209-217	HLA-A*0201	<u>ITDQVPFSV</u> → <u>IMDQVPFSV</u>
	280-288	HLA-A*0201	YLEPGPVTA
	457-466	HLA-A*0201	LLDGTATLRL
	476-485	HLA-A*0201	VLYRYGSFSV
		HLA-A*0301	ALLAVGATK
Tyrosinase (530 aa)	1-9	HLA-A*0201	MLLAVLYLL
	192-200	HLA-B*4403	YEIWRDIDF
	206-214	HLA-A*2402	AFLPWHRLF
	369-377	HLA-A*0201	YMNGTMSQV



Specific activation of PBL *in vivo* by MAA derived epitopes
as demonstrated by *in vitro* testing



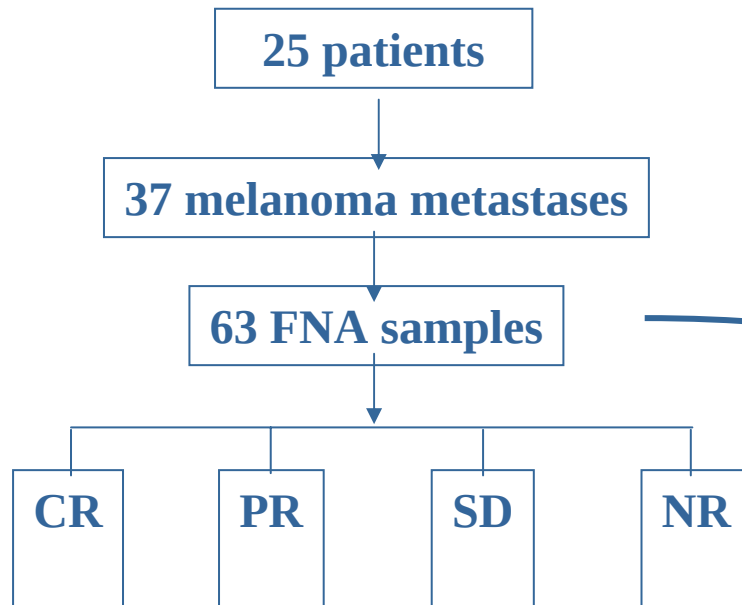
(Cormier et al., Cancer J. Sci Am. 1997) .

Response rate after peptide-based vaccinations against melanoma

	<u>Responses</u>	<u>Patients</u>	<u>%</u>
<u>Treatment:</u>			
MART-1 ₂₇₋₃₅ in IFA	0	20	0
g209-2M in IFA	0	11	0
g209-2M in IFA + IL-2 (720,000 IU/Kg TID)	13	31	42

(Rosenberg et al. Nature Med,1998)

TEST sample



Reference sample:

Mixture of 6 normal donor PBMC

6,108 human
cDNA array

Control sample:

NHEM - Normal Human Epithelial Melanocyte

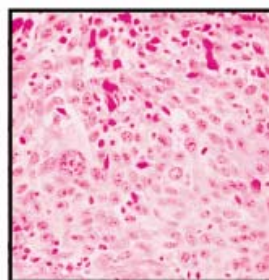
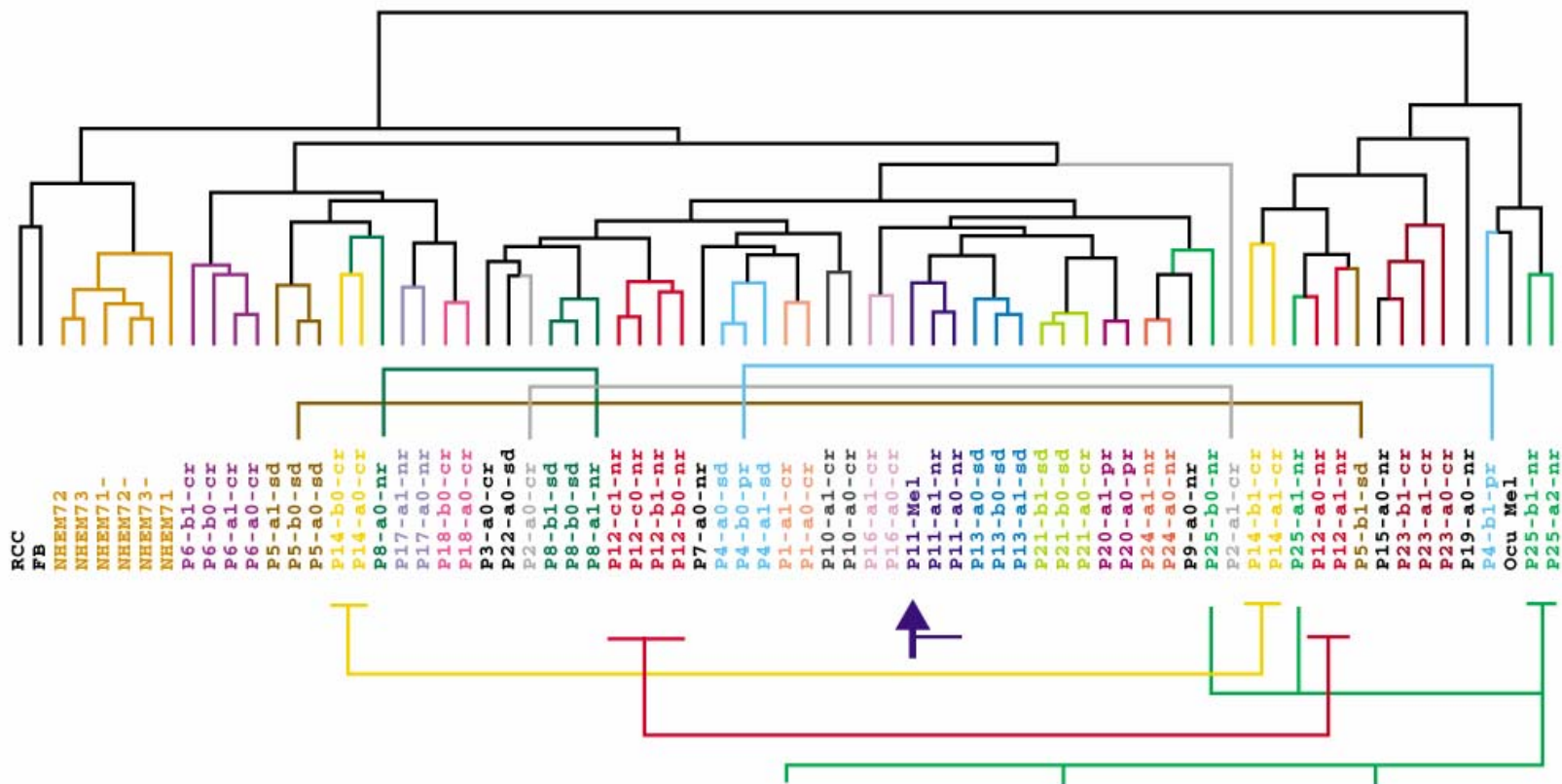
FB - Fibroblast cell line from melanoma metastasis

RCC - Renal carcinoma

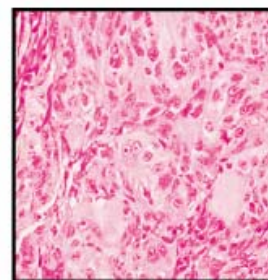
Ocu - Ocular melanoma

Wang et al. Nature Biotech. 2000

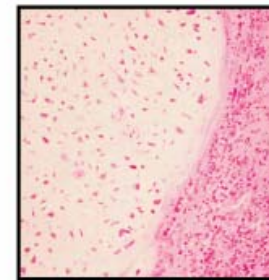
Wang et al. Cancer Res. 2002



60% Epithelioid
Melanoma



20% Pleyomorphic
Transition Zone



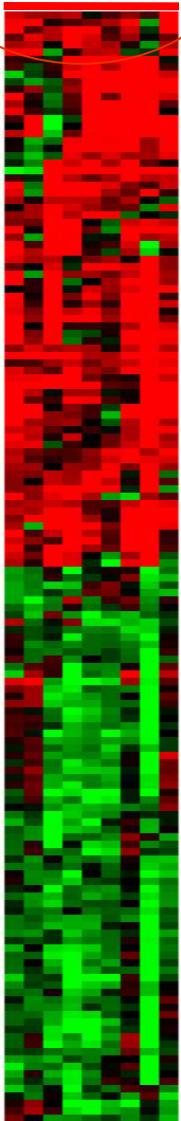
20% Chondrosarcoma

Wang et al. Cancer Res. 2002

Clone ID	Abbrev.	Title	Putative function	Relative expression
Genes that discriminate between pre-treatment melanoma lesions that regressed completely or did not (13 vs 21)				
322961	CAPZB	capping protein (actin filament) muscle Z-line, beta	Cell migration	Enhanced
323917	EHD1	EH domain containing 1	Ligand induced endocytosis	Enhanced
725284	PHKG2	phosphorylase kinase, gamma 2	Kinase	Enhanced
344080	SHMT2	Serine hydroxymethyltransferase mitochondrial precursor	Cell metabolism	Enhanced
269815	INHBA	Inhibin, β A	TGF- β family	Enhanced
136218	TIA1	TIA1 cytotoxic granule-associated RNA-binding protein	CTL-mediated cytotoxicity	Enhanced
504469	ODF2	outer dense fibre of sperm tails 2	Cell migration	Enhanced
345935	MADH	MADH3	TGF- β response regulator	Enhanced
854138	CSNK1E	casein kinase 1, epsilon	DNA replication repair	Enhanced
768496	EBI3	EBI3	Interleukin-12 facilitator	Enhanced
324210	SR-BP1	sigma receptor (SR31747 binding protein 1)	Cell proliferation regulation	Enhanced
796297	KIAA1605	KIAA1605	Unknown	Enhanced
811116	EST	EST	Unknown	Enhanced
323371	APP	Amyloid β (A4) precursor protein)	Intracellular signaling	Enhanced
321739	IRF2	Interferon- γ regulatory factor 2	Interferon expression regulation	Enhanced
43884	PPIF	Peptidylprolyl isomerase F (Cyclophilin F)	Cell metabolism	Enhanced
109316	Serpina3	α 1-antichymotrypsin	Proteinase inhibitor	Enhanced
195458	EST	EST	Unknown	Suppressed
51463	BIRC1	neuronal apoptosis inhibitory protein	Apoptosis regulator	Suppressed
148421	TXK	TXK tyrosine kinase	T cell regulation	Suppressed
1103633	KIAA0515	KIAA0515	Unknown	Suppressed
221846	CHES1	checkpoint suppressor 1	DNA-damage checkpoint	Suppressed
563423	JAK1	JAK1	Interleukin-2 receptor regulation	Suppressed
588915	IFI27	interferon, alpha-inducible protein 27	IFN-induced tumor suppressor	Suppressed
588637	ACTG1	Actin=cytoskeleton γ actin	Cell migration	Suppressed
322160	PTEN	MMAC1=PTEN=Tumor suppressor gene	Putative tumor suppressor	Suppressed
814095	LTA4H	Leukotriene A4 hydrolase	Immediate hypersensitivity	Suppressed
365098	BNIP3L	BCL2/adenovirus E1B 19kD-interacting protein 3-like	Putative tumor suppressor	Suppressed
280752	RBL2	Retinoblastoma-like 2 (p130)	Putative tumor suppressor	Suppressed
240109	FLJ10632	Homo sapiens cDNA FLJ10632	Unknown	Suppressed
1457955	EST	EST	Unknown	Suppressed
142259	FIP2	Tumor necrosis factor α -inducible cellular protein	TNF pathway	Suppressed
240099	EST	EST	Unknown	Suppressed

**Non-specific
immune stim.**

What is the role of interleukin-2



Highest median across experiments: cell
surface, adhesion
inflammatory proteins

MHC class II DR alpha
MHC class II DR beta

Grancalcin Ca²⁺ binding protein in
neutrophils and monocytes
Calgranulin Ca²⁺ binding protein

CD62L L-selectin

CD45

V-CAM-1

CD64

CD29 integrin=beta 1 fibronectin
receptor

(Fibronectin 1)

Keratin 10

IL-1 R

IL-1 receptor antagonist

IL-2 R beta chain

TNF- α induced protein 3

TGF β receptor

Interferon- γ IEF SSP5111upregulated protein
(HSP70)

MxA/interferon induced cellular resistance protein
MxB interferon induced cellular resistance mediator
protein

(Interferon- α inducible protein IFI-6-16)

Guanylate binding protein 1 interferon inducible

IRF-1 interferon regulatory factor-1

IFN induced 56KDa protein

IFN γ receptor alpha chain

Nmi=IL-2 and IFN-g inducible potentiator of STAT

Human insulin like growth factor

C-C chemokine receptor 1

GRO-1 melanoma growth stimulatory activity chemokine

MIG chemokine targeting T cells

(MCP-1)

MCP-3

MIP-1beta

MIP-1 alpha

PARC=DC-CK1 chemokine targeting T cells not monocytes

Monocyte neutrophils elastase inhibitor

IL-8 chemokine

Plasminogen activator urokinase

Primary Goal of this study: **Is it possible to link functional to genetic information using high-throughput technology?**

- **Rationale:**

- Human immunology is a complex discipline encompassing **human polymorphism** and **epigenetic adaptation** to heterogeneous environmental stimuli.
- **Transcriptional and/or post-translational analyses** (i.e. cDNA arrays) yield information about the cellular response to a given situation without segregating genetic predisposition from epigenetic adaptation.
- **Genome wide screening** for genetic variation could lead to the identification of consistent patterns in a given population that could segregate the functional influence of genetic variability from that of epigenetic adaptation.

Jin P and Wang E. Immune polymorphism: from HLA typing to immunogenetic profiling

Wang E and Falus A. Changing paradigm through a genome-based approach to clinical and basic immunology

<http://www.translational-medicine.com>