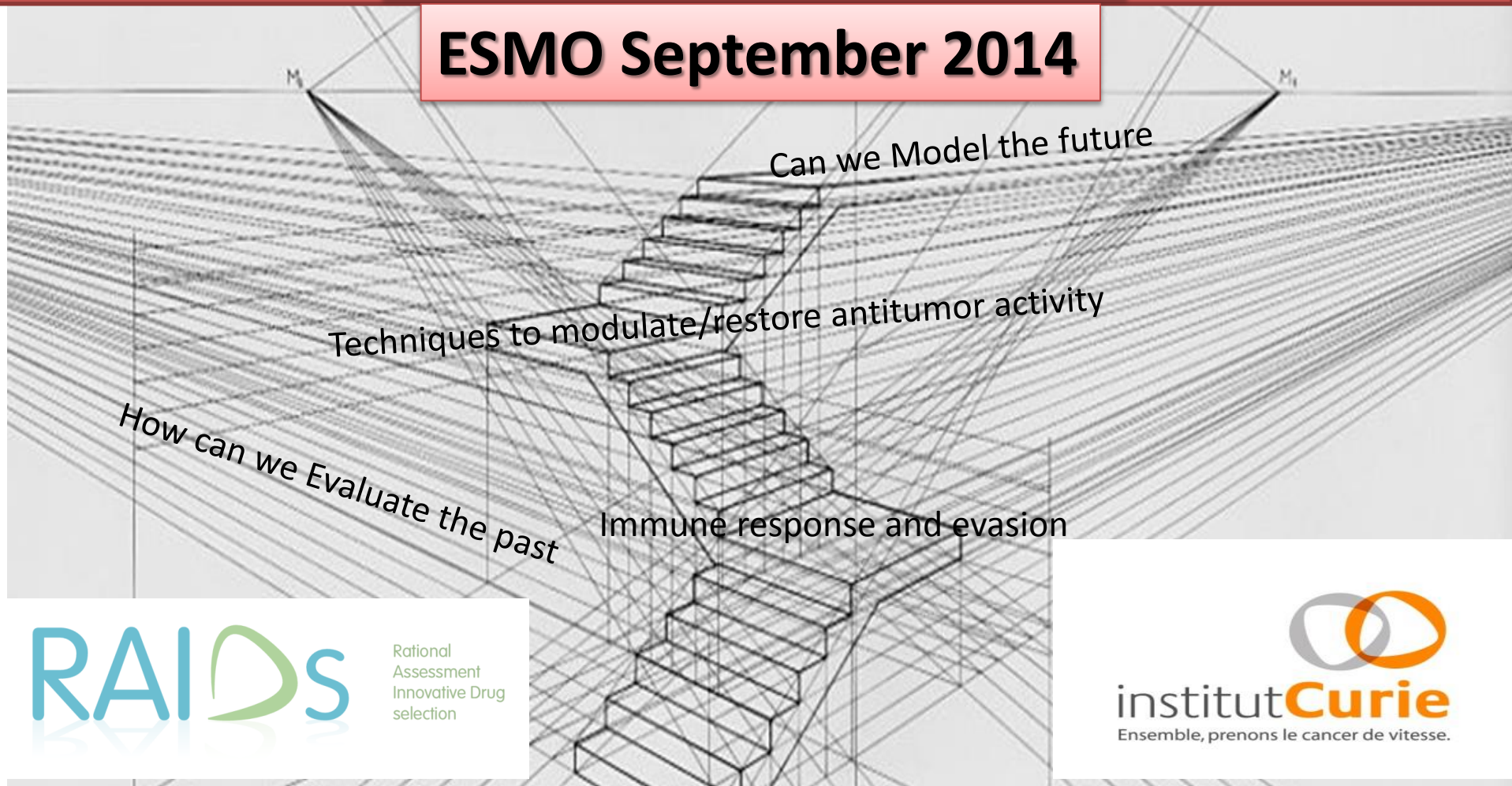
FUNDAMENTAL PRINCIPLES OF ANTITUMOUR IMMUNE RESPONSE

A summary for the clinician

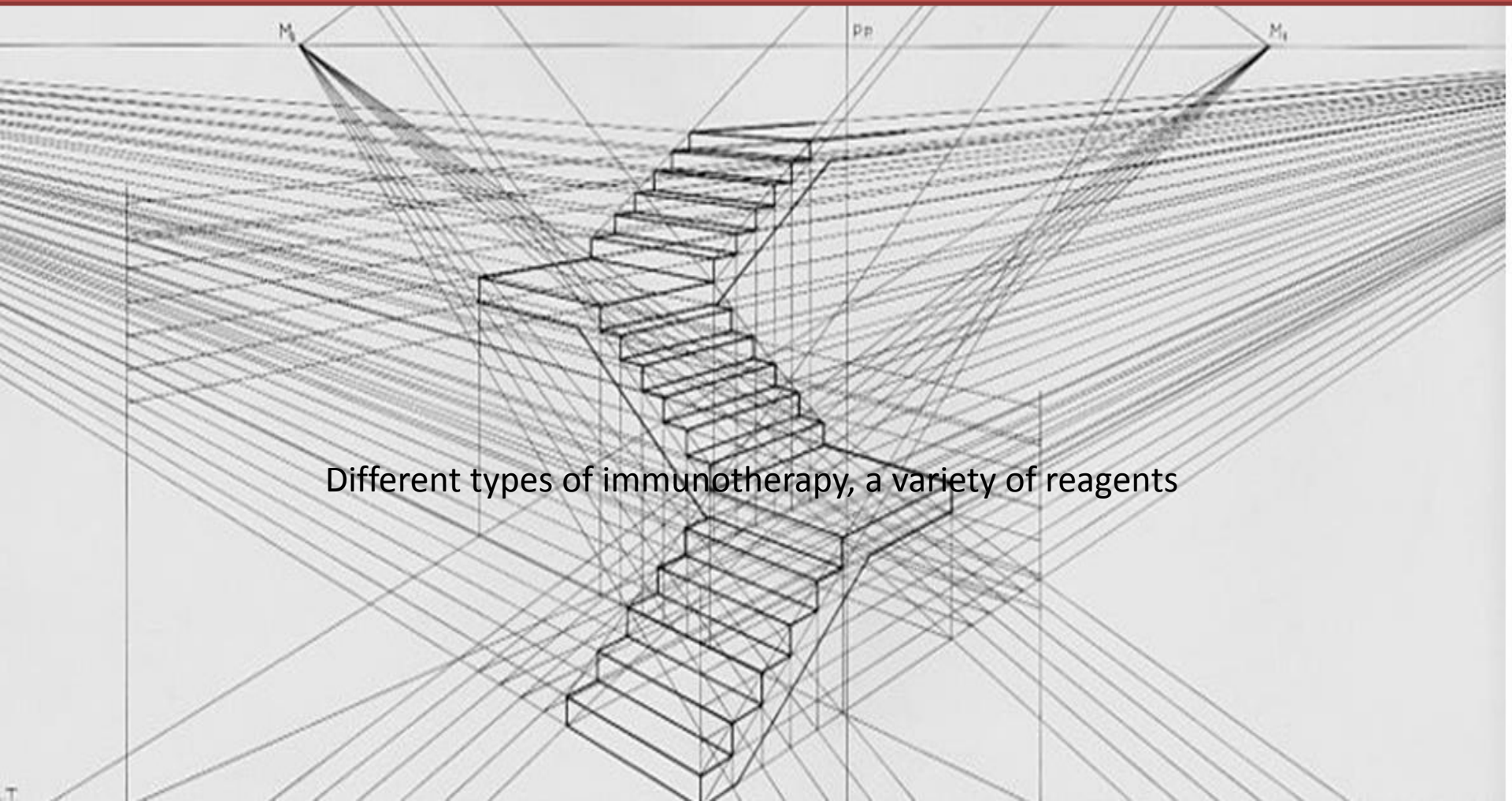
ESMO September 2014



RAIDs
Rational Assessment Innovative Drug selection

institutCurie
Ensemble, prenons le cancer de vitesse.

The 2 crucial questions
Which reagent? Which perspective? How to evaluate the patient?



Different types of immunotherapy, a variety of reagents

nature REVIEWS CLINICAL ONCOLOGY

The POINT group

Original articles published between 2000 and 2014
Search terms: « cancer » , « vaccine », « immunotherapy »

NATURE REVIEWS CLINICAL ONCOLOGY | REVIEW Publis

Therapeutic vaccines for cancer: an overview of clinical trials

Ignacio Melero Gustav Gaudernack Winald Gerritsen Christoph Huber Giorgio Parmiani Suzy Scholl Nicholas Thatcher John Wagstaff Christoph Zielinski Ian Faulkner Håkan Mellstedt

Principals of antitumor immune response

Wright Brothers' first flight

The brothers flew the plane for 12 seconds and covered 120 feet!
Date 17 Dec 1903

A one half scale model of Gustave Whitehead's Number 21, the plane he reportedly flew over Fairfield on the morning of August 14, 1901, on display at the Fairfield Museum and Histopry Center's annual Fall Festival on Sunday, September 12, 2010. The flight,

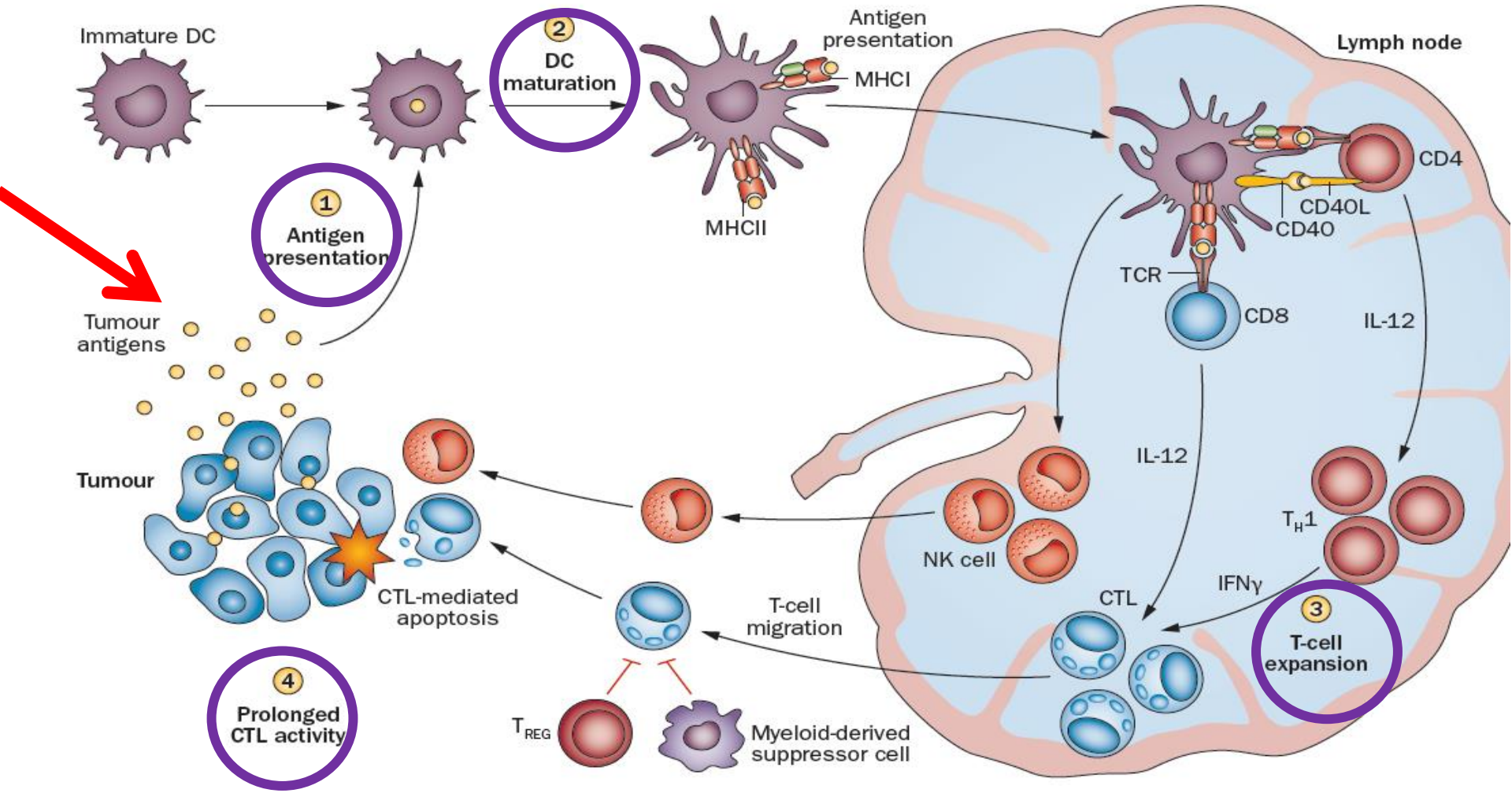
Propulsion

Lift/wings

Balanced center of gravity and weight

CONTROLLED FLIGHT

Prerequisites for immune function in the context of cancer



Principals of antitumor immune response

List of Antigens & Adjuvants

❖ **SHARED ANTIGENS**

- Cancer-testis: BAGE,GAGE,MAGE,NY-ESO-1
- Differentiation antigens: CEA, gp100, Melan-A, PSA, tyrosinase
- Overexpressed antigens: HER2, hTERT, p53, survivin

❖ **UNIQUE ANTIGENS**

- Oncogene associated antigens: β-catenin, HSP70-2/m, KRAS

❖ **SHARED ANTIGENS WITH UNIQUE MUTATIONS**

- Glycans: GM2, MUC1

- **Cytokines/endogenous immunomodulators** GM-CSF, IL12
- **Microbes and microbial derivatives** BCG,CpG,Detox,MPL,poly I:C
- **Mineral salts** Alum
- **Oil emulsions or surfactants** AS02, MF50, MontanideTM, ISA-51, QS-21**,**
- **Particulates** AS04, polylactide co-glycolide, virosomes
- **Viral vectors** Adenovirus, vaccinia, fowlpox

Propulsion may be equated with antigens which represent the fuel to tumor vaccination

ANTIGENS AND ADJUVANTS IN PHASE III CLINICAL TRIALS

What has been achieved?

EARLY DAYS: MANY FAILED PHASE III TRIALS

ABANDONED AT INTERIM ANALYSIS

WHICH INFORMATION COULD BE GAINED?

Start Year	Vaccine
1980s	OncoVAX [1]
1994	Vaccinia Melanoma Oncolysate
1998	Canvaxin
-	Melacine
2002	Theratope[2]
2002	Gastrimmune
2002	Oncophage[3]
2004	Panvac-VF
-	MyVax
-	Favid
2004	GVAX[4]
-	GMK

Subgroup: Stage II colon cancer

Subgroup: Women on hormonal treatment following chemotherapy

Subgroup: Patients with M1a and M1b substages on high-dose vaccine

Subgroup: Patients with Halabi-predicted survival > 18 months

ITT group show no OS (and/or TTP) benefit

BUT

efficacy demonstrated in retrospective subgroup analyses

[1]Hanna, et al. Vaccine 2001;19:2576-82 [2] The Pharmaletter, June 2003. [3]Testori ,et al. J Clin Oncol 2008; 26(6):955-62 [4]Higano, et al. Genitourinary Cancer Symposium 2009. Abstract No. LBA150

By clinical trial standards: Not valid to go forward

nature REVIEWS CLINICAL ONCOLOGY

AR

view

NATURE REVIEWS CLINICAL ONCOLOGY | REVIEW

41
phase 2 and phase 3 trials

14 with
significant numbers of patients
>1000 pts: 4
>400 pts: 2
>100 pts: 8

Therapeutic vaccines for cancer: an overview of clinical trials

Ignacio Melero Gustav Gaudernack Winald Gerritsen Christoph Huber Giorgio Parmiani Suzy Scholl Nicholas Thatcher John Wagstaff Christoph Zielinski Ian Faulkner Håkan Mellstedt

Principals of antitumor immune response

CONCLUSION ON « PROPULSION »

ANTIGENS AND ADJUVANTS IN PHASE III CLINICAL TRIALS: *mostly NS but some highlights*

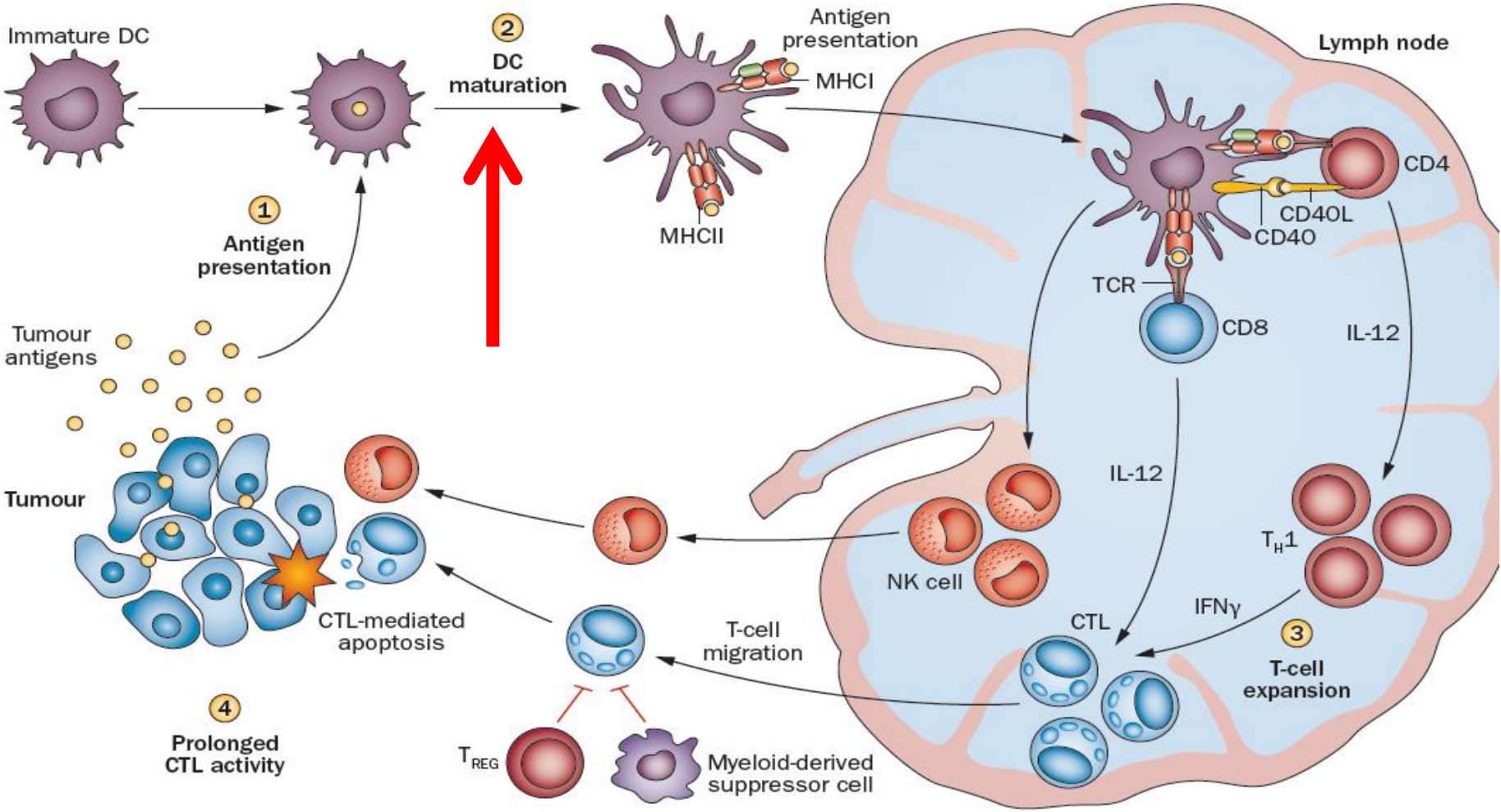
Combination therapy

Early stage cancers

Endpoint: OS rather than PFS

Dendritic cells developed outside of the tumor

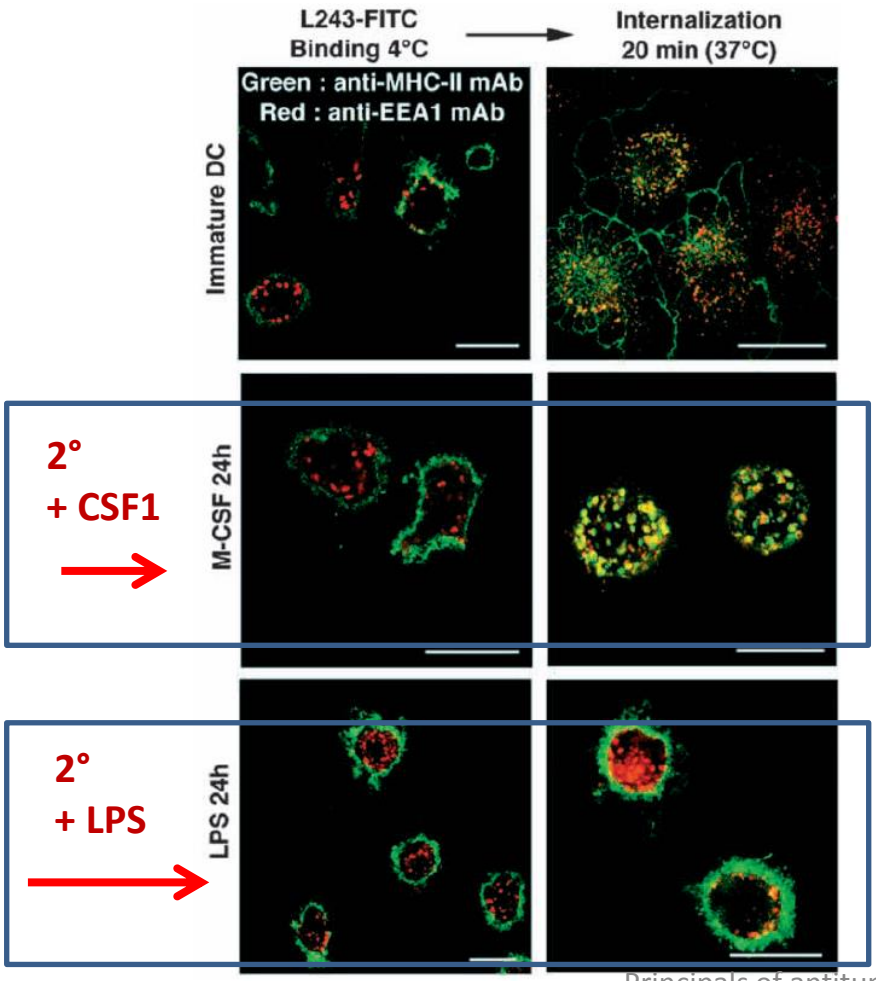
Prerequisites for immune function in the context of cancer



Principals of antitumor immune response

Dendritic cell maturation *in vitro / in vivo*

1° IL4 and GM-CSF



Ex: PROVENGE

Salamero lab - J Cell Sci 2000

Modulation of MHC class II transport and lysosome distribution by macrophage-colony stimulating factor in human dendritic cells derived from monocytes

Carole L. Baron[1], Graça Raposo[2], Suzy M. Scholl[3], Huguette Bausinger[4], Danielle Tenza[2], Alain Bohbot[5], Pierre Pouillart[3], Bruno Goud[1], Daniel Hanau[4] and Jean Salamero[1,*]

[1]UMR 144 CNRS-Institut Curie, Laboratoire des Mécanismes Moléculaires du Transport Intracellulaire, 26, rue d'Ulm, Paris, France
[2]UMR 144 CNRS-Institut Curie, Laboratoire de Microscopie Electronique, 26, rue d'Ulm, Paris, France
[3]Institut Curie, Service de Medecine Oncologique, 26, rue d'Ulm, Paris, France
[4]INSERM E 99-08, Laboratoire d'histocompatibilité, ETS Strasbourg, France
[5]Service d'Onco-Hématologie, Hôpital de Hautepierre, Strasbourg, France
*Author for correspondence (e-mail: salamero@curie.fr)

Accepted 19 December 2000
Journal of Cell Science 114, 999-1010 © The Company of Biologists Ltd

red: early endosomes
green HLA class 2

Tumor Associated MACROPHAGES

ARE DISTINCT FROM

Mammary Tissue MACROPHAGES

Mammary tissue macrophages and TAMs are distinct

As the tumor size increases, from 65mm3 to 300mm3

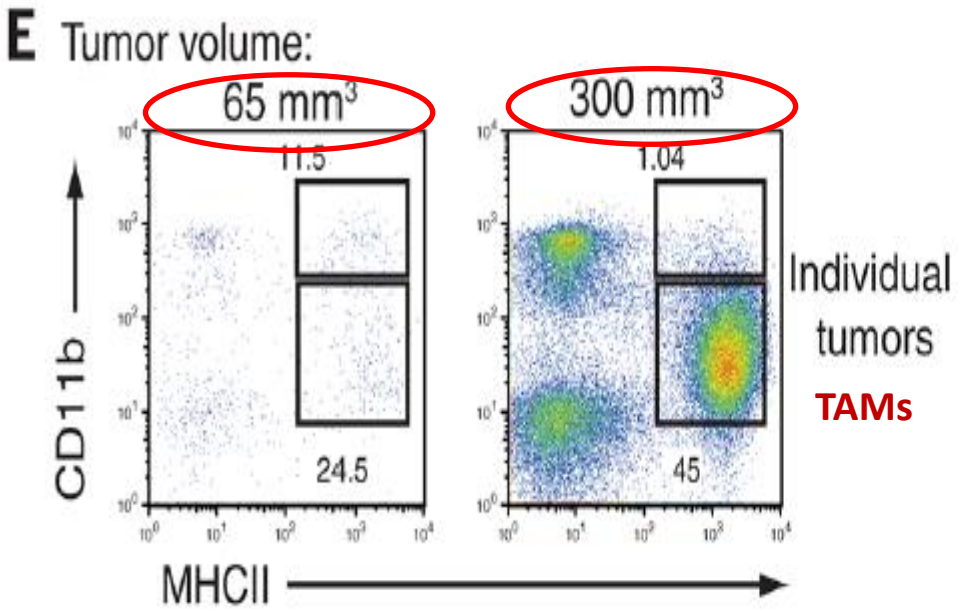
the amount of Tumor Associated Macrophages increases

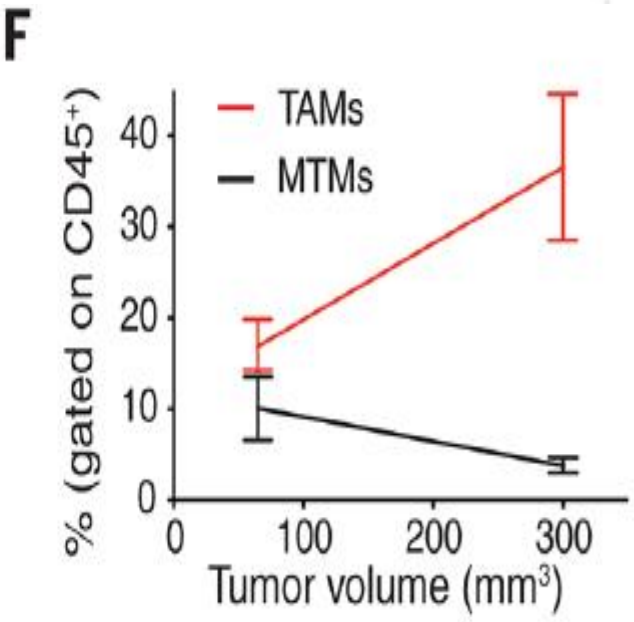
while mammary tissue macrophages are lost

Sciencexpress

The Cellular and Molecular Origin of Tumor-Associated Macrophages

Ruth A. Franklin,[1,2] Will Liao,[3] Abira Sarkar,[1] Myoungjoo V. Kim,[1,2] Michael R. Bivona,[1] Kang Liu,[4] Eric G. Pamer,[1] Ming O. Li[1]*





IF YOU DEPLETE T A M (BUT NOT MTM)

YOU RESTORE TIL RESPONSES

AND

SUPPRESS TUMOR GROWTH

TO BECOME and REMAIN AIRBORNE

- Avoidance of heavy crosswinds
- Through in vitro expansion of DCs and TILs in the laboratory

Past achievements in avoiding crosswinds

- ***In vitro* Dendritic cell expansion**
  - Sipuleucel T (PROVENGE^{R} – DENDREON)
    - FDA approved autologous dendritic cell vaccine
    - designed to target the prostate PAP antigen
  - **To treat minimally symptomatic/asymptomatic metastatic Prostate Cancer**
  - **Needs minimum treshold value of CD54 expression a marker of DC activation**
- **Many ongoing trials based on *in vitro* DC cell expansion**
  - **Prostate**
  - **Ovary**
  - **Etc..**

Table 2. Completed phase III trials: immunotherapy and therapeutic cancer vaccines in prostate cancer.

Agent	Primary endpoint	Comments
Sipuleucel-T (two identically designed, randomized, double-blind, placebo-controlled trials) D9901, D9902A	Time to disease progression	Improved OS, no improvement in TTP Integrated analysis (n = 225) Treatment group with 33% reduction in risk of death (HR 1.50; 95% CI 1.10–2.05; p = 0.011)
Sipuleucel-T (IMPACT)	OS	Improved OS compared with placebo (n = 512): 25.8 *versus* 21.7 months; HR 0.78; 95% CI, 0.61–0.98 Led to FDA approval in 2010
GVAX (VITAL-1)	OS	GVAX compared with docetaxel (HR 1.01)

Therapeutic Advances in Vaccines **By H Sing and J Gulley** *Review*

Therapeutic vaccines as a promising treatment modality against prostate cancer: rationale and recent advances

Ther Adv Vaccines

2014, Vol. 2(5) 137–148

DOI: 10.1177/2051013614539478

Table 1. Selected combination immunotherapy trials for patients with prostate cancer.

Phase	Agent	NCT number	Study design	Primary endpoint	Expected completion date
II	Sipuleucel-T/ ADT	NCT01431391	Patients with nonmetastatic prostate cancer randomized to receive sipuleucel-T before or after ADT	Immune response	August 2014
II	Sipuleucel-T/ Abiraterone	NCT01487863	Patients with metastatic CRPC randomized to receive sipuleucel-T plus abiraterone and prednisone, administered either sequentially or concurrently	Immune response (including PAP-specific T-cell response); safety	July 2015
II	Sipuleucel-T/ Enzalutamide	NCT01981122	Patients with metastatic CRPC randomized to receive sipuleucel-T plus enzalutamide, administered either sequentially or concurrently	Immune response	September 2015

By H Sing and J Gulley

Therapeutic vaccines as a promising treatment modality against prostate cancer: rationale and recent advances

B. Harpreet Singh and James L. Gulley

Ther Adv Vaccines
2014, Vol. 2(5) 137–148
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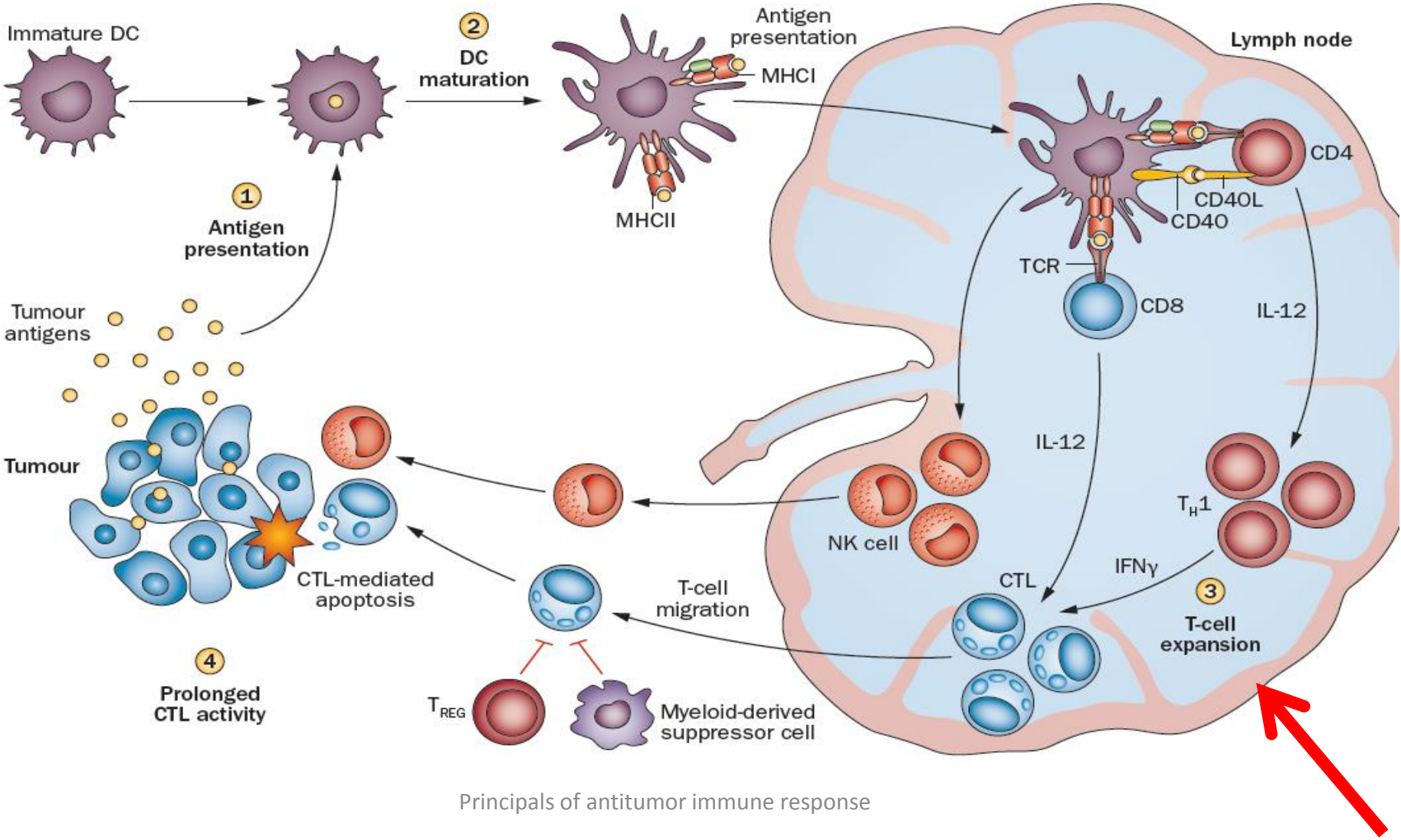
Prerequisites for immune function in the context of cancer



Principals of antitumor immune response

T cell expansion *in vitro: solid tumors*

- ***In vitro*** **autologous T cell expansion and reinfusion**

Adoptive T cell therapy with expanded cultures of tumour infiltrating lymphocytes

- **Remarkable clinical responses in melanoma** *Dudley JCO 2008 (n=93)*
- **RR 50-70% (if assoc chemo + TBI)**
- **Selected patients**

- ***In vitro*** **T cell receptor preparation and reinfusion**

Adoptive T cell therapy with autologous engineered T cells transduced with an anti-MAGE-A3 TCR. *Morgan, J Immunother 2013*

- **Substantial regression in 5/9 pts.**
- **Neurotoxicity in 3/9**
- **Selected patients**

CONCLUSION ON
IN VITRO EXPANSION
of DC & T cells

FDA approval of DENDREON^{R}

DC & T cell expansion are powerful tools

Patient selection

Presently expensive to manufacture

Propulsion

Lift/wings

Balanced center of gravity and weight

CONTROLLED FLIGHT

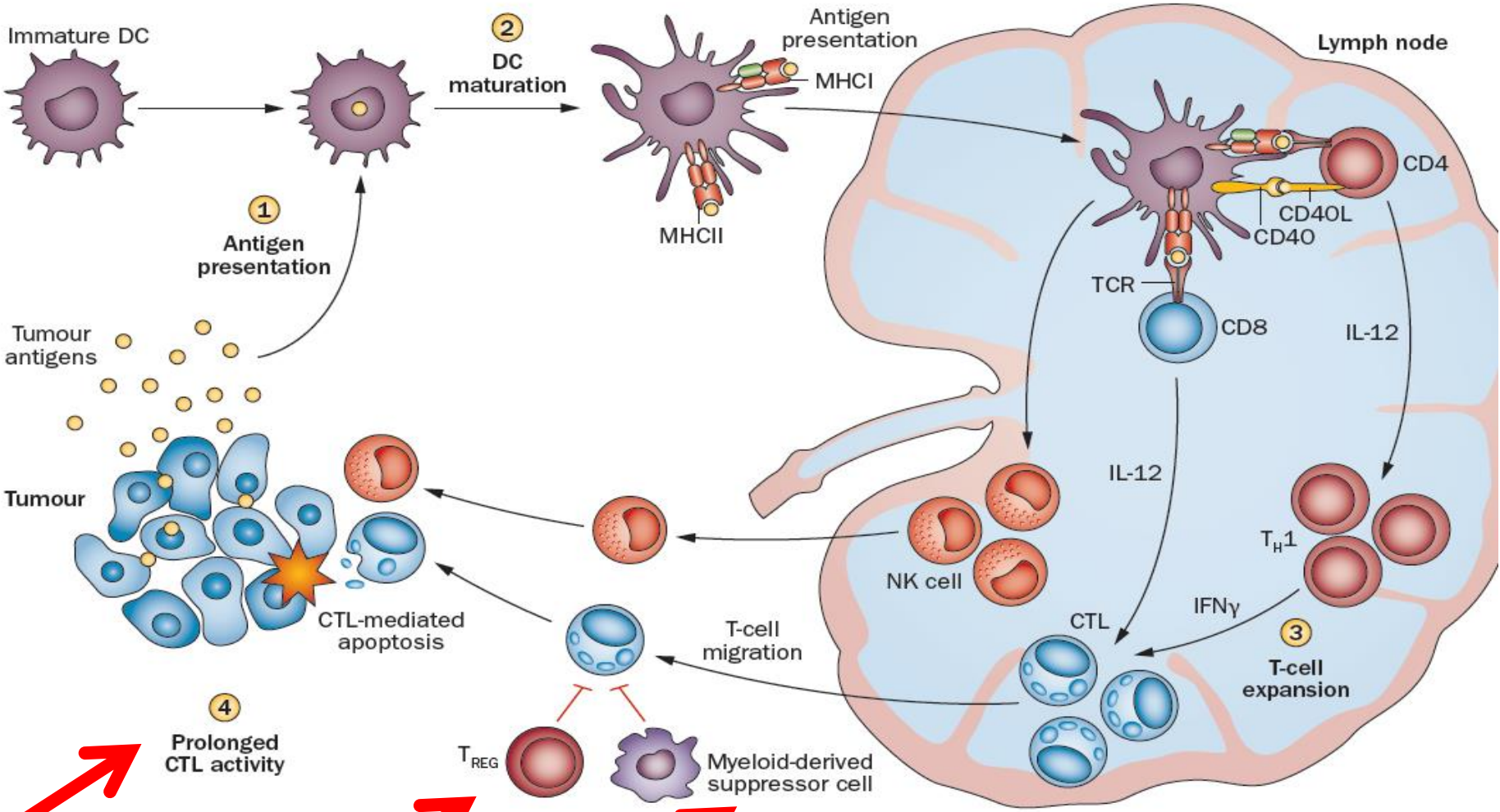
ACHIEVEMENTS ON CHECKPOINT MODULATION

In the normal immune function

Activity is counterbalanced by negative regulators such as CTLA4

CTLA4: role is to shut down excessive immune activation to avoid auto immunity

Prerequisites for immune function in the context of cancer



Prolongation of T cell lytic activity

Modify check points	Prevent/decrease T-regulatory cells	Decrease myeloïd suppressor activity
▪ Stimulation of activating Rcptrs ▪ Blockage of Inhibitory receptors/ligands PD-L1 , PD-1, CTLA4,	Active standard therapy - Chemotherapy, - Hormonetherap - Radiotherapy - Targeted therapy	DC maturation *in vivo* – Block TAM – Block CSF1/CSF1 R

To remain airborne:

balance and centre of gravity

Weighting Model for a Horsa glider

II	Prostvac	NCT00020254	Patients with nonmetastatic	Time to progression	Completed

Therapeutic vaccines as a promising treatment modality against prostate cancer: rationale and recent advances

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B. Harpreet Singh and James L. Gulley

	GVAX		randomized to receive docetaxel or GVAX		
III	Ipilimumab/ XRT	NCT00861614	Patients with metastatic CRPC post chemo randomized to ipilimumab/ XRT compared with placebo/XRT	Overall survival	Completed
II	153Sm-EDTMP (Quadramet)/ PSA-TRICOM	NCT00450619	Patients with metastatic CRPC randomized to ^{153}Sm-EDTMP with or without PSA-TRICOM	Progression-free survival at 4 months	Completed
I	Ipilimumab/ GVAX	NCT01510288	Patients with metastatic CRPC treated with GVAX and escalating doses of ipilimumab	Safety	Completed
I	Ipilimumab/ PSA-TRICOM	NCT00113984	Patients with metastatic CRPC treated with PSA-TRICOM and escalating doses of ipilimumab	Safety	Completed

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 28, 2012 VOL. 366 NO. 26

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.

"APPROXIMATELY 1/4 TO 1/5 PATIENTS TREATED WITH ANTI–PD-1 ANTIBODY HAD OBJECTIVE RESPONSES WITH DURABILITY

IN HEAVILY PRETREATED PATIENTS WITH DIVERSE TUMOR TYPES"

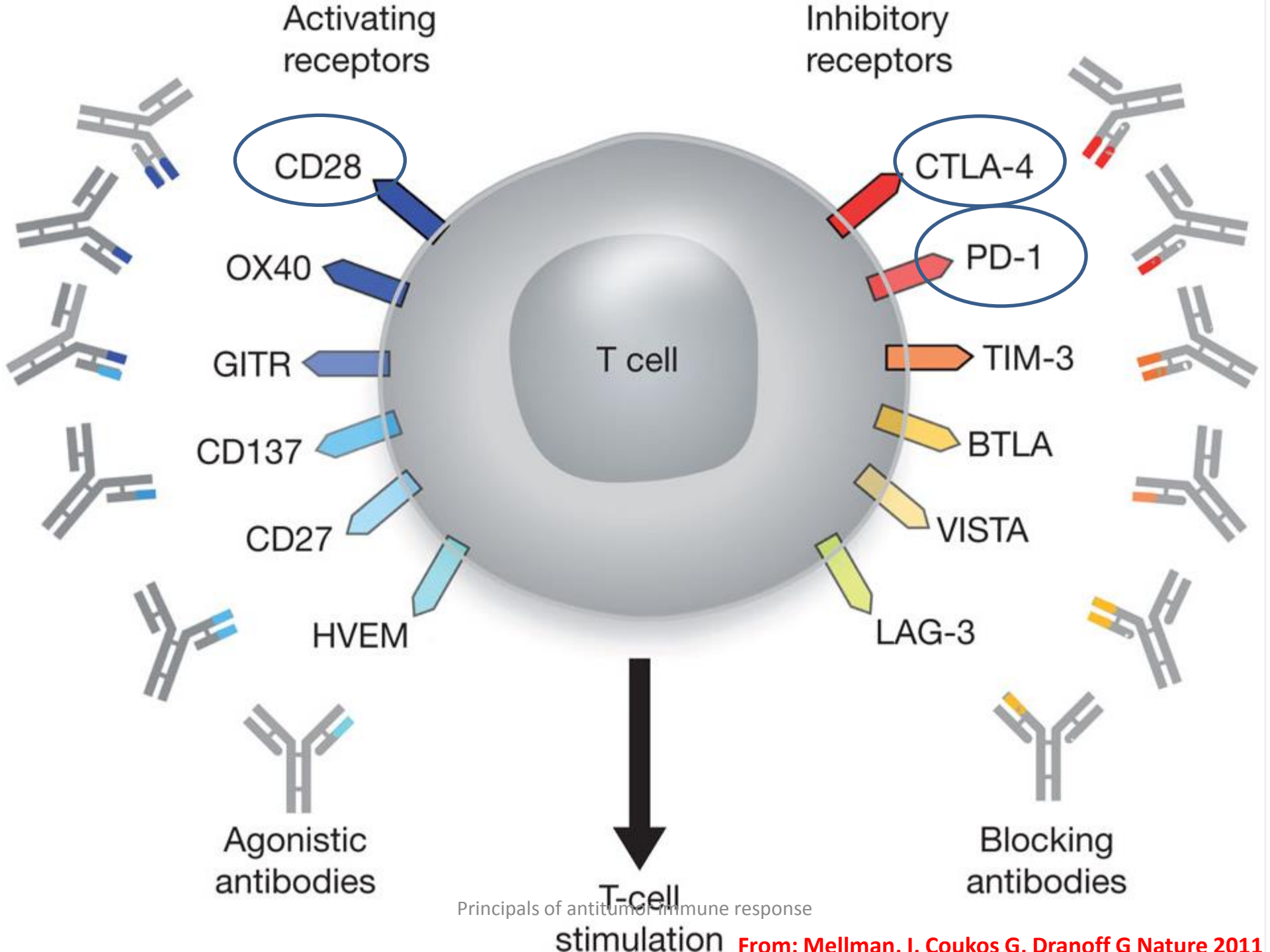
Tolerance of PD1/PDL blocade

296 patients treated up to early 2012: No MTD!

Drug-related adverse events consistent with immune-related causes

Grade 3 or 4: 14% of patients

3 deaths (pulmonary toxicity)



From: Mellman, I, Coukos G, Dranoff G Nature 2011

The NEW ENGLAND JOURNAL of MEDICINE

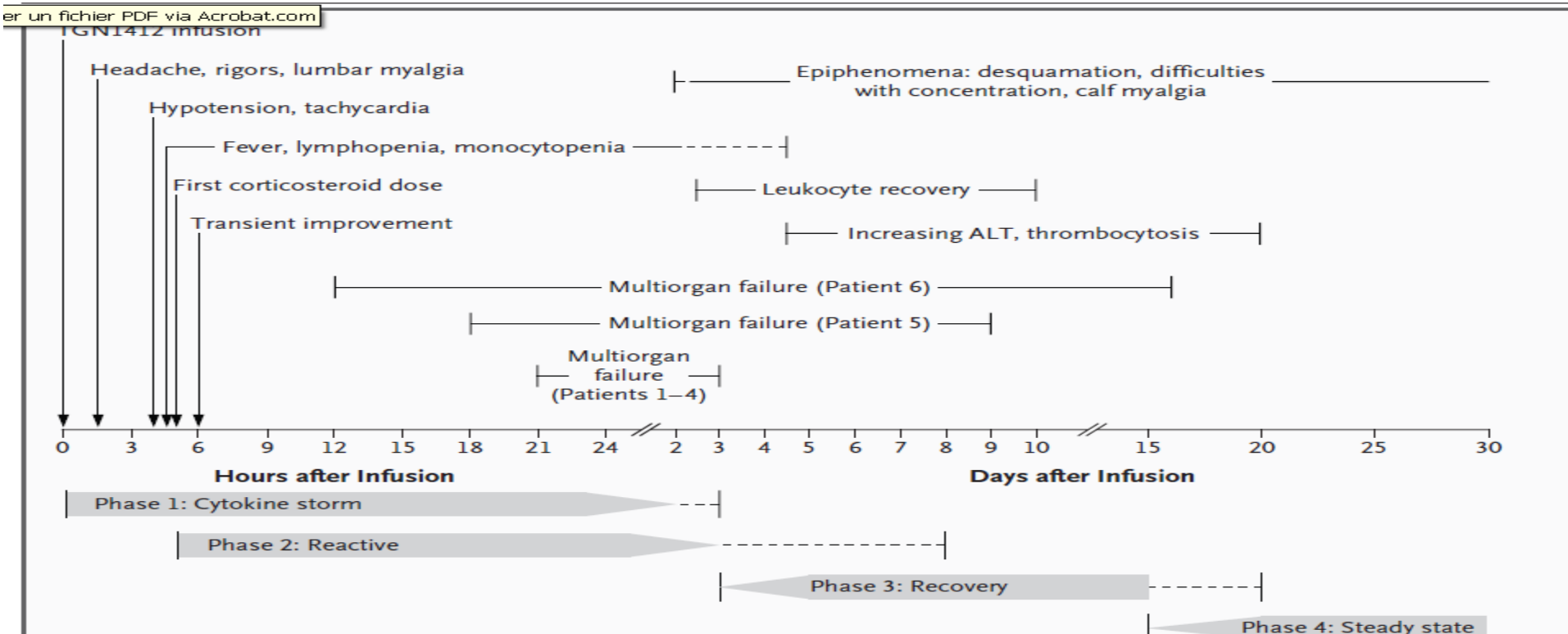
BRIEF REPORT

A word of caution

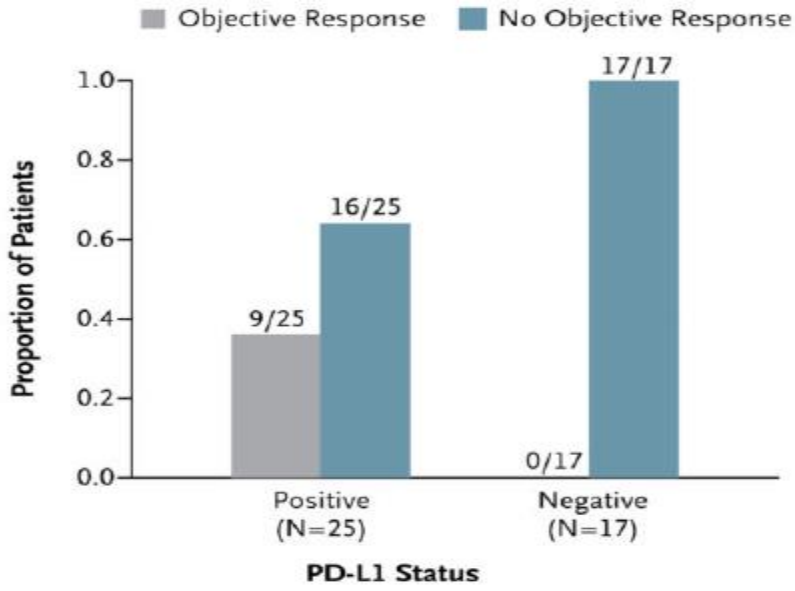
Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412

N Engl J Med 2006;355:1018-28.

Ganesh Suntharalingam, F.R.C.A., Meghan R. Perry, M.R.C.P.,
Stephen Ward, F.R.C.A., Stephen J. Brett, M.D., Andrew Castello-Cortes, F.R.C.A.,



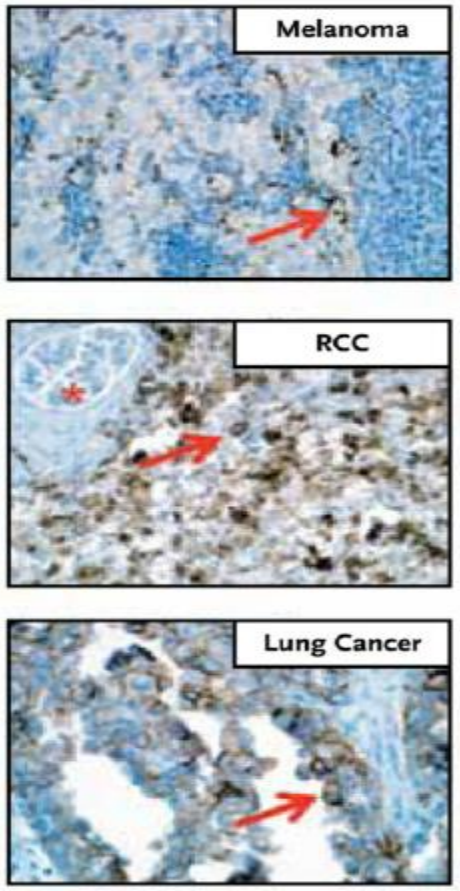
Finally: patient selection for checkpoint blocade treatment?



Association between Pretreatment Tumor PD-L1 Expression and Clinical Response

Response Status	PD-L1–Positive	PD-L1–Negative	Total
		number (percent)	
Objective response	9 (36)	0	9 (21)
No objective response	16 (64)	17 (100)	33 (79)
All	25	17	42

P=0.006 for association by Fisher's exact test



CONCLUSION ON CHECKPOINT MODIFYERS IN CLINICAL TRIALS

VERY HIGH clinical interest

Ease of administration: off the shelf

Tolerance appears acceptable: immune related AE

Not clear whether PDL1 expression is a useful biomarker for patient selection

2nd crucial question

How to track immune set up in the patient?

RAIDs

Rational
Assessment
Innovative Drug
selection

Website: http://www.raids-fp7.eu/

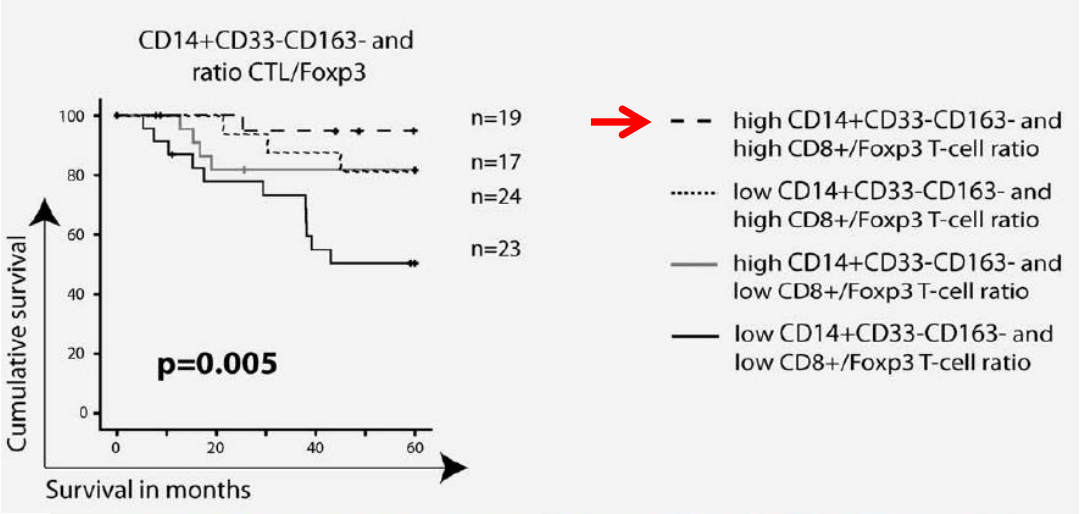
FAVORABLE CELL PHENOTYPE

TIL AND MYELOID CELLS AT TUMOR SITE

- **Effective DC**

  'M1 type'

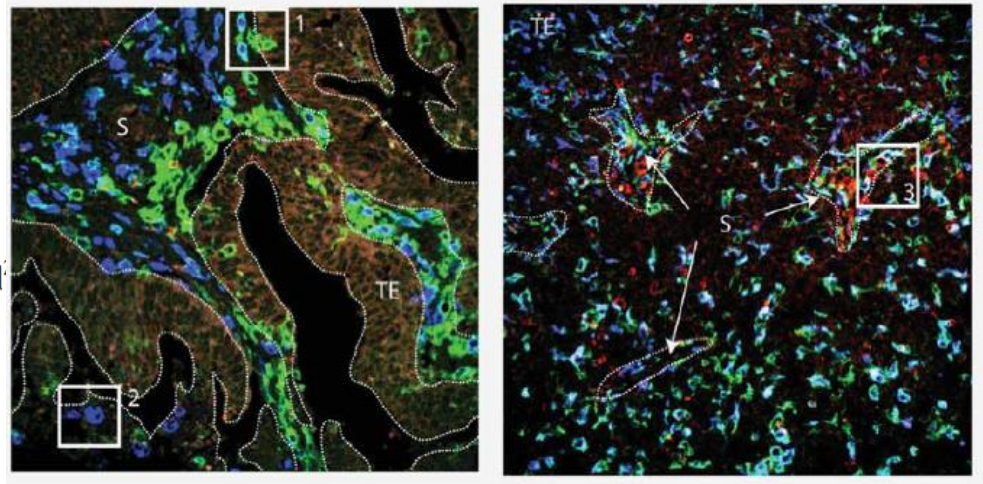
- **High CD8/Treg ratio**



Tumor-infiltrating CD14-positive myeloid cells and CD8-positive T-cells prolong survival in patients with cervical carcinoma

P.J. de Vos van Steenwijk[1], T.H. Ramwadhdoebe[2], R. Goedemans[2], E.M. Doorduijn[2], J.J. van Ham[2], A. Gorter[3], T. van Hall[1], M.L. Kuijjer[3], M.I.E. van Poelgeest[1], S.H. van der Burg[2*] and E.S. Jordanova[3*]

[1] Department of Gynecology, Leiden University Medical Center, Leiden, The Netherlands
[2] Department of Clinical Oncology, Leiden University Medical Center, Leiden, The Netherlands
[3] Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands



International Journal of Cancer 2013

Principals of antitumor immune resp

CD14 CD33 CD163

Mrs H. patient 207

Individual patient success story

Journal of Biomedicine and Biotechnology • 2003:3 (2003) 194–201 • PII. S111072430320704X • http://jbb.hindawi.com

RESEARCH ARTICLE

Metastatic Breast Tumour Regression Following Treatment by a Gene-Modified Vaccinia Virus Expressing MUC1 and IL-2

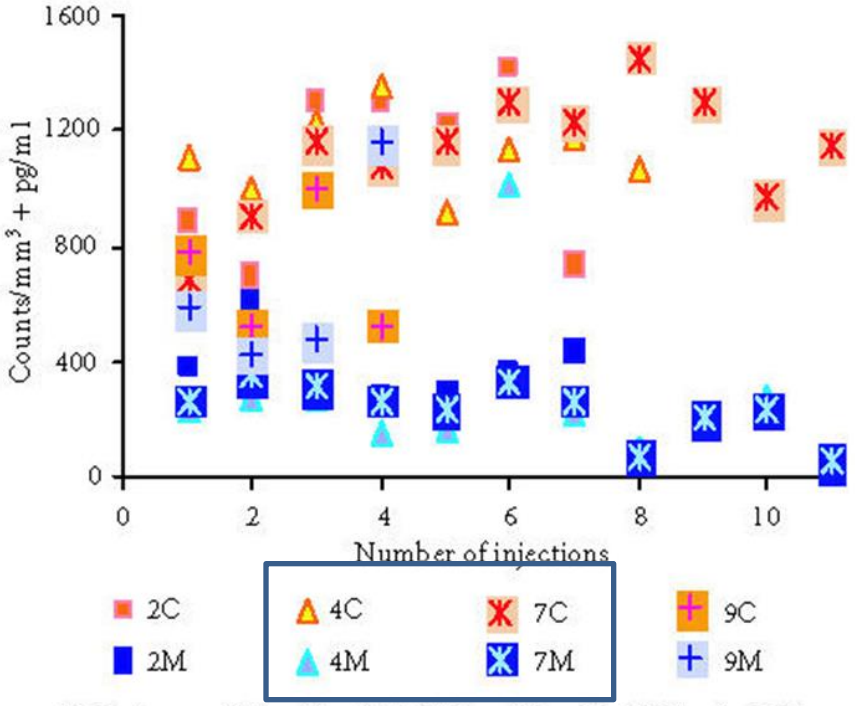
TG 4010

Susy Scholl,[1]* Patrick Squiban,[2] Nadine Bizouarne,[2] Martine Baudin,[2] Bruce Acres,[2] Silvia von Mensdorff-Pouilly,[3] Moira Shearer,[4] Philippe Beuzeboc,[1] S. Van Belle,[5] B. Uzielly,[6] Pierre Pouillart,[1] Joyce Taylor-Papadimitriou,[4] and David Miles[4]

[1]*Institut Curie, Paris Cedex 05, France*
[2]*Transgene S.A., Strasbourg, France*
[3]*Free University Hospital, De Boelelaan 1117, 1081 HV, Amsterdam, Netherlands*
[4]*Cancer Research UK Breast Cancer Biology Group, Guy's Hospital, London, UK*
[5]*University Hospital, Gent, Belgium*

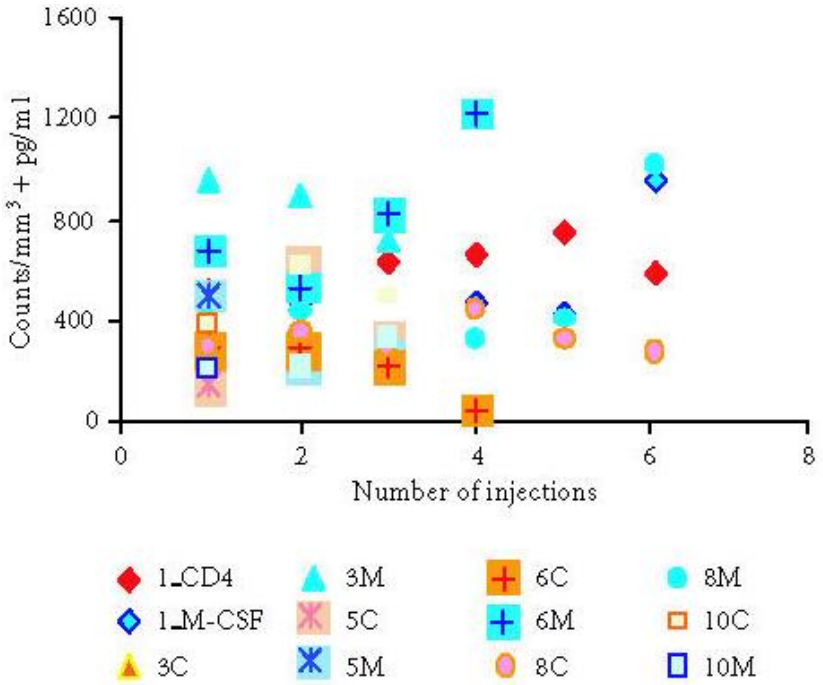
VARIATIONS IN CIRCULATING CD4+ T CELLS AND CSF1 SERUM LEVELS IN 10 PATIENTS

- **Pattern: CD4 high – CSF1 low**



(a) Patients with baseline high CD4 and low M-CSF levels: PR in patients 204 and 207.

- **Pattern: CD4 low – CSF1 high**



(b) Patients with baseline low CD4 and/or high M-CSF levels.

2 Partial Responses;
1 patient (207) alive and well at +15 years

Rapid progressors

VARIATIONS IN CIRCULATING CD4+ T CELLS AND INCREASE IN ANTITHYROÏD ANTIBODIES

TABLE 3. Variations of CD4 levels and antithyroid antibodies over the course of treatment in patient 207.

injection #	date	CD4	CD4/CD8	CA153	anti-TPO	anti-nuclear	anti-DNA	T4	TSH
		counts/mm^3	ratio	U/ml	U/ml	Inverse ratio	U/ml	ng/L	μU/ml
BL	20/01/99	680		26	179	0	0		
1	28/01/99			23		0	0	10.7	1.18
2	18/02/99	908		18		0	0	10.3	1.94
3	11/03/99	1160	4.7	18		0	0		
4	01/04/99	1081	5.2	17		0	0		
5	17/05/99	1172	5.6	16		0	0	12	2.92
6	28/06/99	1305		18		80	14	15.2	2.23
7	09/08/99	1224	4.7	17		160	15		
8	20/09/99	1444	5.5	18	11529	320	13	5.8	51.29
9	02/11/99	1345	3.5	18	11052			11.9	9.14
10	13/12/99	966	4.7	18	6667	260	7	12	0.97

PATIENT 207

TUMOR MEASUREMENTS OVER THE COURSE OF 1 YEAR

TABLE 1. Tumor measurements in patient 207.

Liver lesion	January 11	March 3	May 7	August 6
Segment VII	19 × 19	18 × 18	16 × 16	11 × 11
Segment VI	28 × 24	28 × 22	26 × 22	19 × 19
Cupole	20 × 20	15 × 20	12 × 14	4 × 4

Maximal diameter at surgery Feb 2000

9

20

5*

*Histologically No tumor

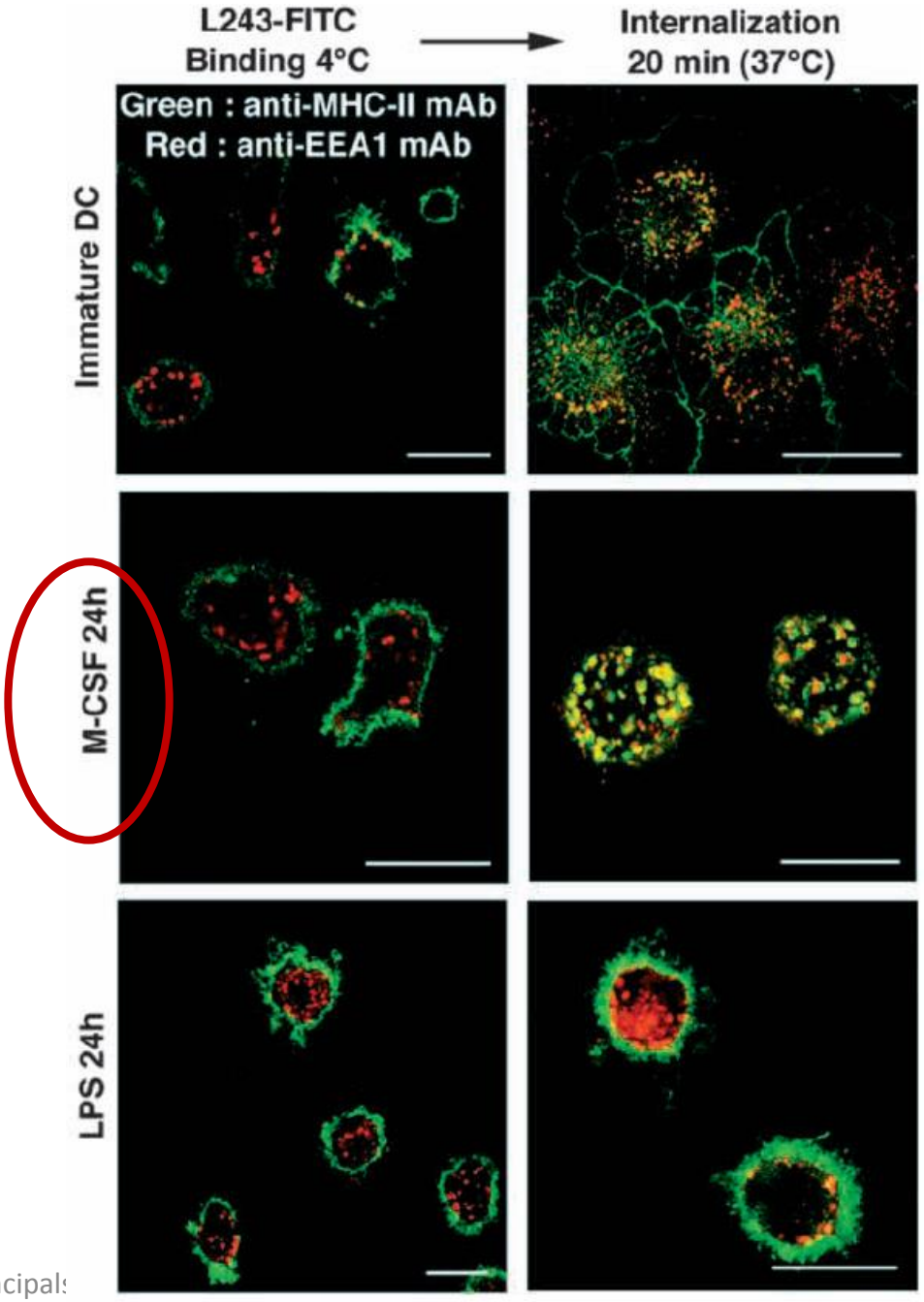
Maximal response August 1999

PATIENT 207

In vitro studies on DC and macrophage differentiation

CSF1 is a key macrophage differentiation marker and abundant in tumors

The assessment of levels in the tumor micro environment and in the circulation may give valuable information on how the tumor microenvironment is geared



Future perspectives
: expanding and folding wings at leisure

The TF-X™

TF-X™ is the practical realization of the dream of countless visions of the future; it is designed to be the flying car for all of us. In order to achieve this long-sought-after vision, Terrafugia will focus the TF-X™ program with clear goals that enhance the safety, simplicity, and convenience of personal transportation. We believe these goals are achievable today.

Future plane: Hoverbike

The *Tyrannos*
gets ready for take-off

- My co speakers will now take you through important aspects of

  - immune evasion
  - how therapeutic immunomodulation can restore antitumor immunity

THE END

Table 1 | Active immunotherapies in phase III development*

Immunotherapy	Targeted antigens	Adjuvants/ immune modulators	Study population	*n*	Outcomes
Prostate cancer					
Autologous cell vaccine: sipuleucel-T, Provenge® DC	PAP	GM-CSF	Metastatic, castration-resistant prostate cancer	512	OS: 25.8 months vs 21.7 months (HR PFS: 3.7 months vs 3.6 months (HR 0. T-cell response in 73.0% vs 12.1% of pa
Allogeneic tumour cell vaccine: GVAX	Tumour cell	GM-CSF	Castration-resistant prostate cancer	626	OS: 20.7 months vs 21.7 months with prednisone (HR 1.03; $P=0.78$)‡
Allogeneic tumour cell vaccine: GVAX	Tumour cell	GM-CSF	Castration-resistant prostate cancer	408	OS: 12.2 months in combination with d 14.1 months docetaxel plus prednisone $P=0.0076$)§
Breast cancer					
Peptide vaccine: Theratope	Sialyl-Tn	KLH COMBI !	Metastatic breast cancer, in remission after first-line chemotherapy	1,028	Median OS: 23.1 months vs 22.3 mont With concomitant endocrine therapy, OS vs 25.4 months ($P=0.005$) Median TTP: 3.4 months vs 3.0 months With concomitant endocrine therapy: 10 6.3 months ($P=0.078$)
Lung cancer					
Peptide vaccine: tecemotide (L-BLP25) COMBI !	MUC1	Liposomal monophosphoryl lipid A plus cyclophosphamide	Unresectable stage III NSCLC; after chemo-radiotherapy	1,239	Median OS: 25.6 months vs 22.3 mont $P=0.123$); OS with concurrent chemoth 30.8 months vs 20.6 months (HR 0.78 OS with sequential chemotherapy: 19.4

Peptide vaccine: GSK1572932A	MAGE-A3	Liposomal AS15	Completely resected stage IB–II NSCLC	182	Trial terminated owing to failure to meet primary end points of extended DFS. Not possible to identify gene signature predicting benefit
Allogeneic tumour cell vaccine: belagenpumatucel-L, Lucanix™	Tumour cell	Anti-TGF-β	Stage IIIB–IV NSCLC	532	Median OS: 20.3 months vs 17 months (HR 0.94; $P=0.594$) Non-adenocarcinoma: 19.9 months vs 12.3 months (HR 0.55; $P=0.036$)
Melanoma					
Peptide vaccine	gp100	IL2 plus Montanide™ ISA51	Locally-advanced stage III or stage IV melanoma	185	OS: 17.8 months vs 11.1 months ($P=0.06$) PFS: 2.2 months vs 1.6 months ($P=0.08$) T-cell responses in 7 of 37 (19%) patients Higher levels of $CD4^+foxp3^+$ cells in patients with clinical response ($P=0.01$)
Peptide vaccine: GSK 2132231A	MAGE-A3	QS-21	Resected melanoma	1,349	Failed to meet primary end point of DFS; ongoing for end point of DFS in patients with predictive gene signature
Pancreatic cancer					
Peptide vaccine: GV1001	Telomerase	GM-CSF	Locally-advanced and/or metastatic pancreatic cancer	1,062	OS: 8.4 months (concurrent with chemotherapy) and 6.9 months (sequential chemotherapy) vs 7.9 months with chemotherapy alone (NS)
Colorectal cancer					
Autologous tumour cell vaccine: OncoVAX®	Tumour cell	BCG	Resected stage II–III colon cancer; after resection	254	42% reduction in the risk of recurrence and/or death ($P=0.032$); greatest effect in stage II disease with 60% reduction in risk of recurrence and/or death ($P=0.007$) and 54% reduction in risk of death
Haematological malignancies					
Autologous anti-idiotype vaccine	Idiotype	KLH	Advanced follicular lymphoma, with complete response after chemotherapy	177	PFS: 23.0 months vs 20.6 months ($P=0.256$) ≥1 blinded vaccination: 44.2 months vs 30.6 months ($P=0.047$)