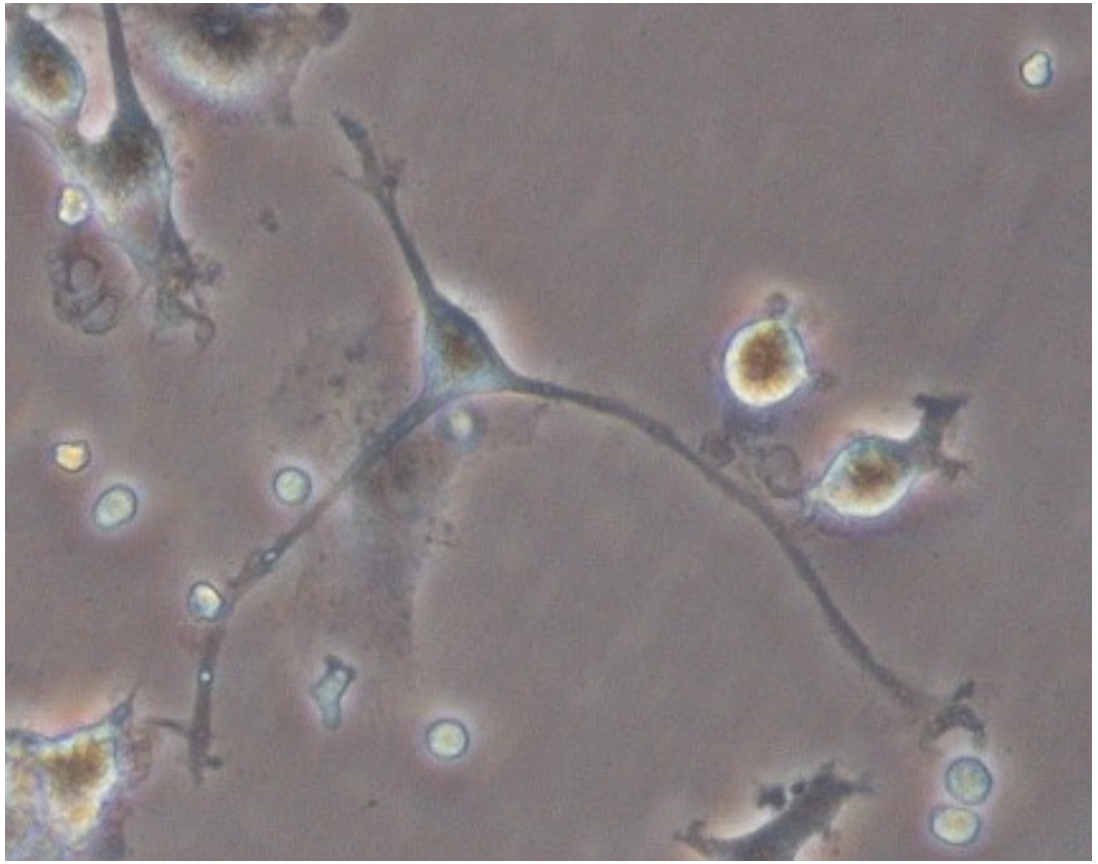
Dendritic cells-based cancer immunotherapy
from conception to clinical application

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FAPESP France Week 2025

IDENTIFICATION OF A NOVEL CELL TYPE IN PERIPHERAL LYMPHOID ORGANS OF MICE

I. Morphology, Quantitation, Tissue Distribution*

By RALPH M. STEINMAN‡ and ZANVIL A. COHN

(*From The Rockefeller University, New York 10021*)

(Received for publication 19 January 1973)

During the course of observations on the cells of mouse spleen that adhere to glass and plastic surfaces, it was clear that this population was quite heterogeneous. In addition to mononuclear phagocytes, granulocytes, and lymphocytes, we noticed a large stellate cell with distinct properties from the former cell types. In this paper, we describe the morphology, quantitation, and tissue distribution of this novel cell as identified in vitro. In following papers, we will further characterize it with respect to its functional properties in vitro, as well as its localization and properties *in situ*.

SUMMARY

A novel cell type has been identified in adherent cell populations prepared from mouse peripheral lymphoid organs (spleen, lymph node, Peyer's patch). Though present in small numbers (0.1–1.6% of the total nucleated cells) the cells have distinct morphological features. The nucleus is large, refractile, contorted in shape, and contains small nucleoli (usually two). The abundant cytoplasm is arranged in processes of varying length and width and contains many large spherical mitochondria. In the living state, the cells undergo characteristic movements, and unlike macrophages, do not appear to engage in active endocytosis. The term, dendritic cell, is proposed for this novel cell type.

Proc. Natl. Acad. Sci. USA
Vol. 75, No. 10, pp. 5132–5136, October 1978
Immunology

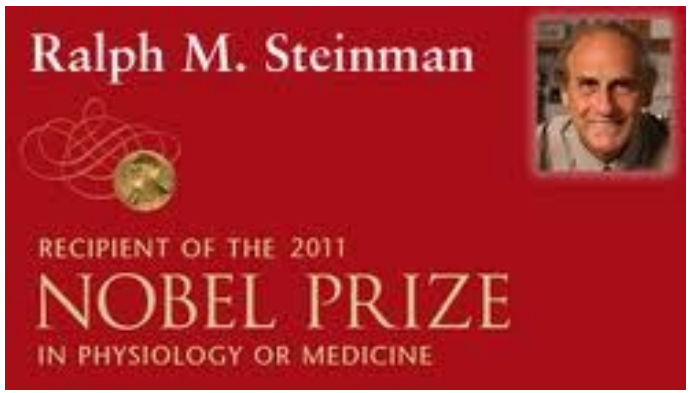
Lymphoid dendritic cells are potent stimulators of the primary mixed leukocyte reaction in mice

(major histocompatibility complex/T and B lymphocytes/macrophages/adherent cells)

RALPH M. STEINMAN AND MARGARET D. WITMER

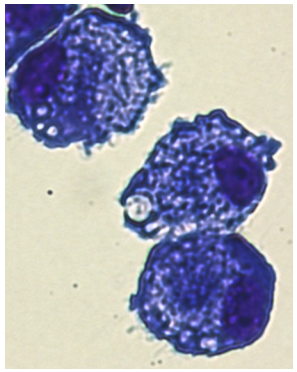
Department of Cellular Physiology and Immunology, The Rockefeller University, New York, New York 10021

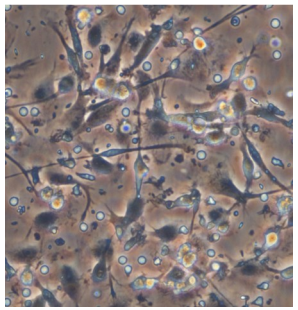
Communicated by Zanvil A. Cohn, July 21, 1978



DC sense the environment and change their functional status

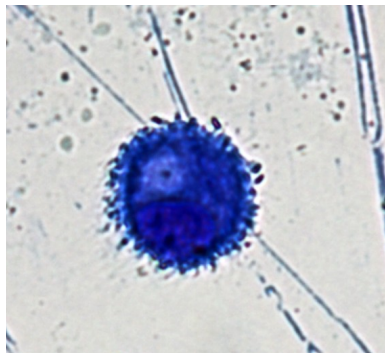
Immature DC

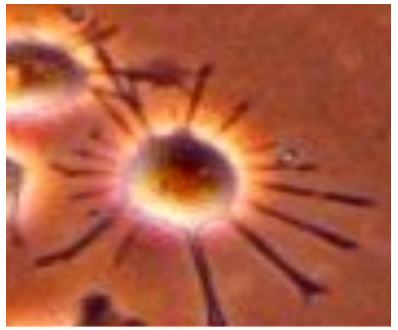


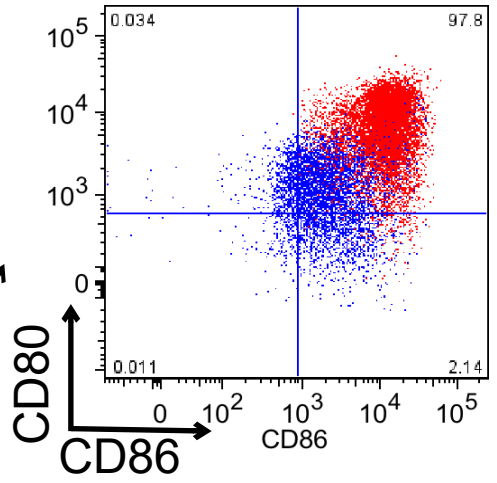


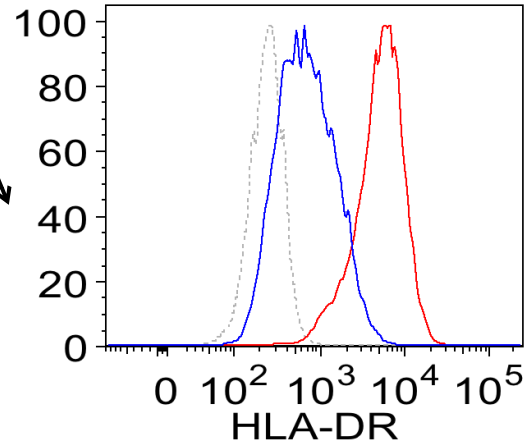
Homeostatic imbalance

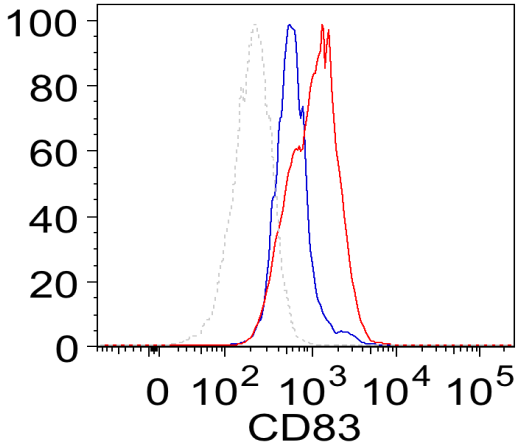
Mature DCs







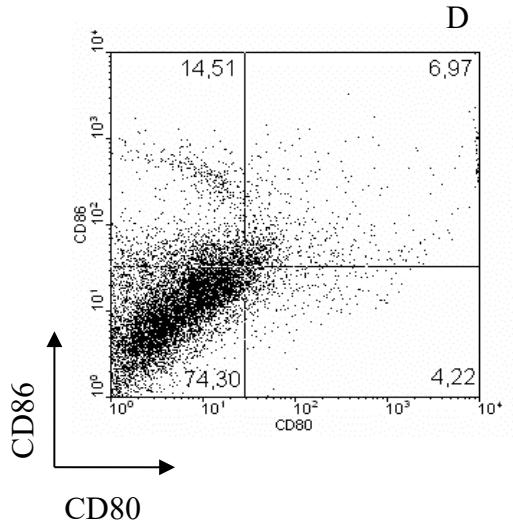


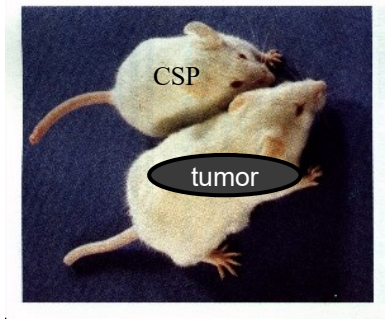


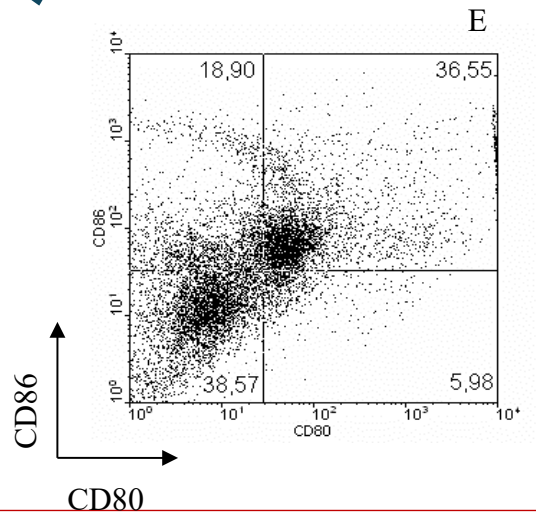
DC recognize even “emotional” stresses as homeostatic imbalances

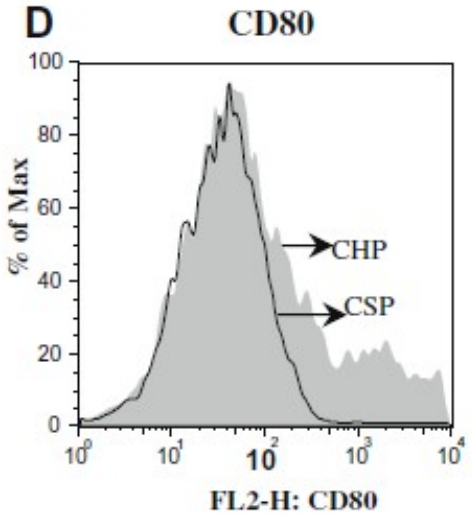


Spleen resident DC
(in vivo)









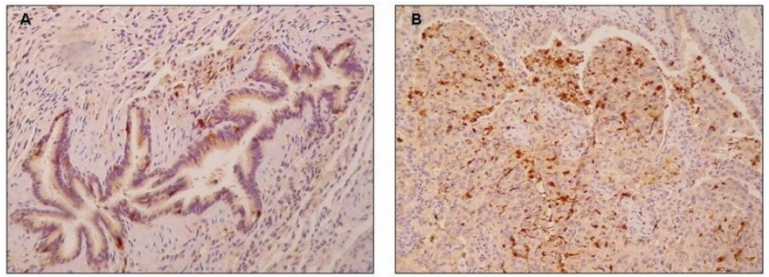
Tomiyoshi, M. Y. et al. (2009). Cohabitation with a B16F10 melanoma-bearer cage mate influences behavior and dendritic cell phenotype in mice. *Brain, Behavior, and Immunity*, *23*(4), 558–567

Within tumors, DC are dysfunctional

- Altered distribution

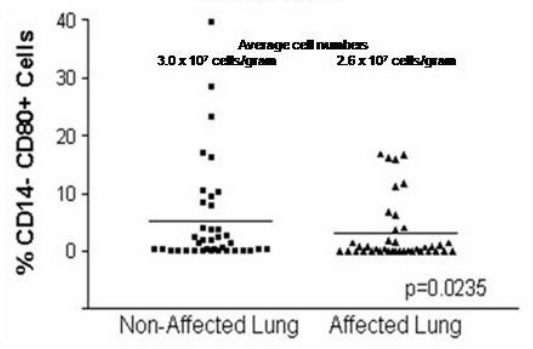
Baleeiro, R. B. et al. (2008). High frequency of immature dendritic cells and altered in situ production of interleukin-4 and tumor necrosis factor-alpha in lung cancer. *Cancer Immunology, Immunotherapy : CII*, *57*(9), 1335–1345.

Lung Tumor



(S100+ cells)

- Defective activation



- Altered "subtypes"

	Lung	Tumor	P
CD1a	6.2	39.3	0.0371
S-100	27.5	59.3	0.0177
CD68	172.4	298.8	0.0108
Mast cells	0.5	2.9	0.0522

IDO+ DC => Treg

Rodrigues CP et al. (2016). Tolerogenic IDO+ Dendritic Cells Are Induced by PD-1-expressing Mast Cells. *Front. Immunol. 7:9*.

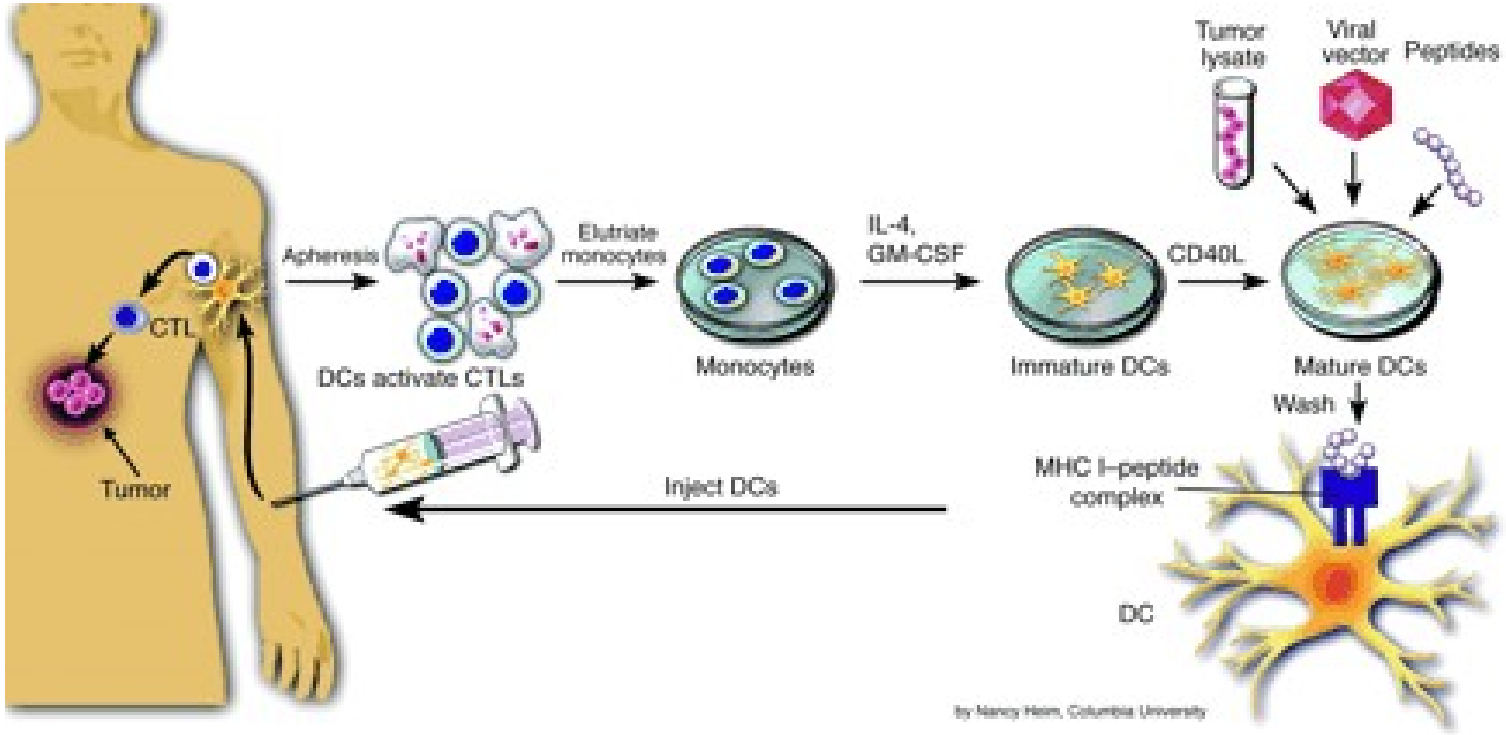
A path to active cancer immunotherapy?

Efficient Presentation of Soluble Antigen by Cultured Human Dendritic Cells Is Maintained by Granulocyte/Macrophage Colony-stimulating Factor Plus Interleukin 4 and Downregulated by Tumor Necrosis Factor α

By Federica Sallusto*‡ and Antonio Lanzavecchia*

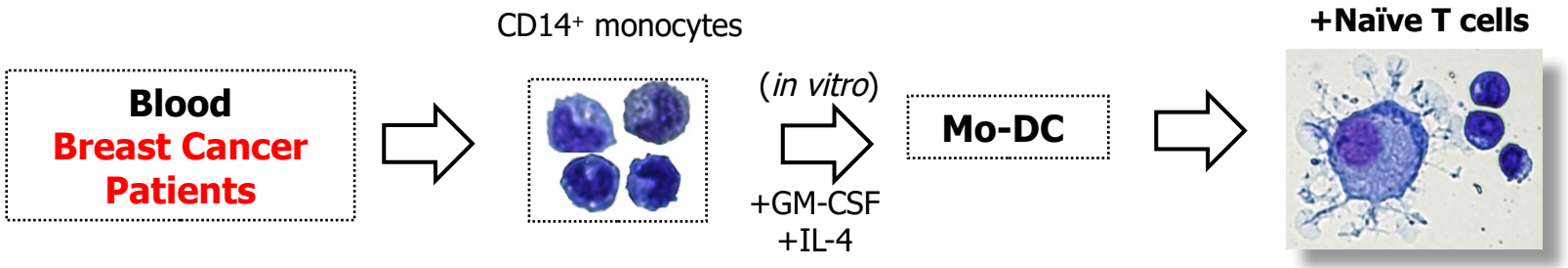
*From the *Basel Institute for Immunology, CH-4005, Basel, Switzerland; and the ‡Department of Immunology, Istituto Superiore di Sanità, I-00161, Rome, Italy*

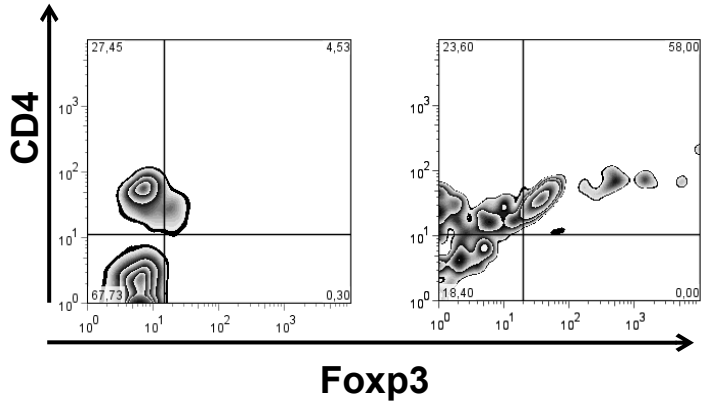
J. Exp. Med. Volume 179 April 1994 1109-1118

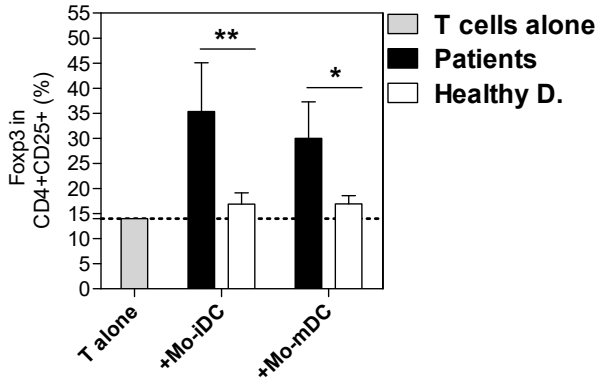


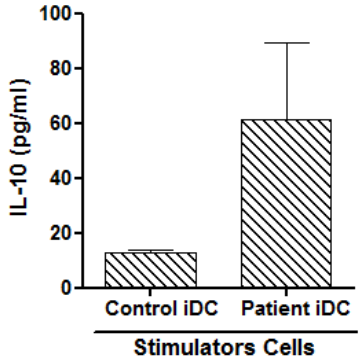
Berzofsky et al , Journal of Clinical Investigation, 113:1515, 2004

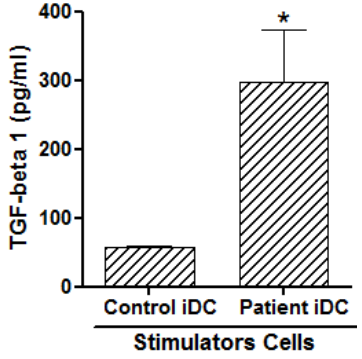
But cancer patients' monocyte-derived DC are biased

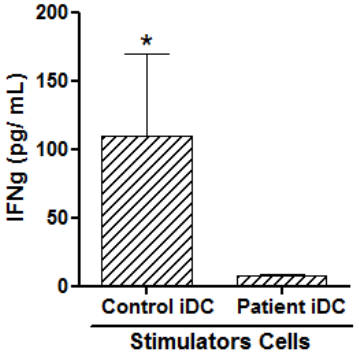








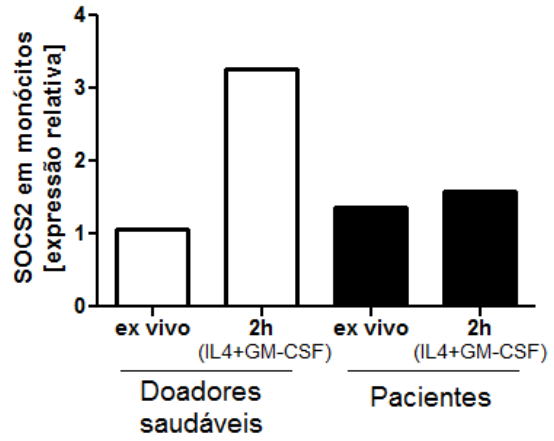


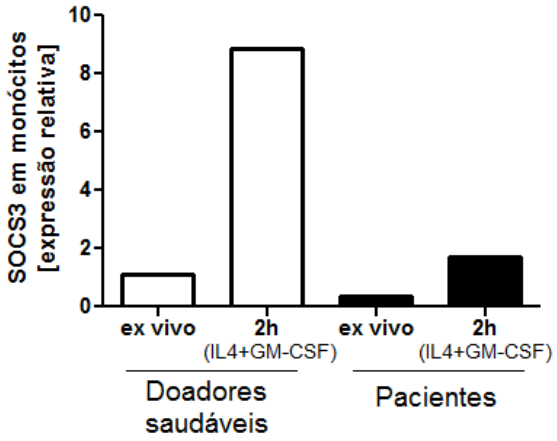


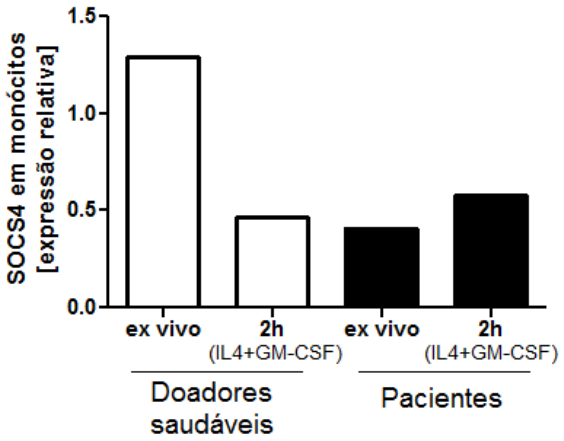
Ramos, R. N. et al. 2012. "Monocyte-Derived Dendritic Cells From Breast Cancer Patients Are Biased to Induce CD4+CD25+Foxp3+ Regulatory T Cells.." *Journal of leukocyte biology* 92(3):673–82.

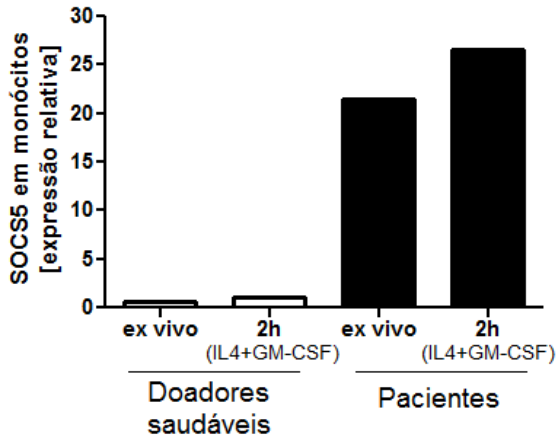
Ramos, R. N. *et al.* CD163+ tumor-associated macrophage accumulation in breast cancer patients reflects both local differentiation signals and systemic skewing of monocytes. *Clinical & translational immunology* **9**, e1108 (2020).

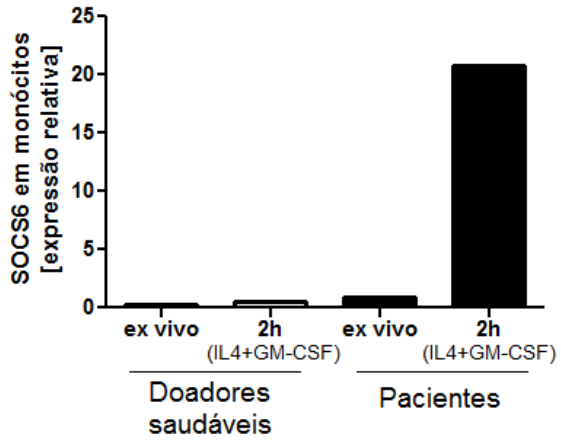
“Suppressors of cytokine signalling” (SOCS) are expressed differentially in cancer patients monocytes



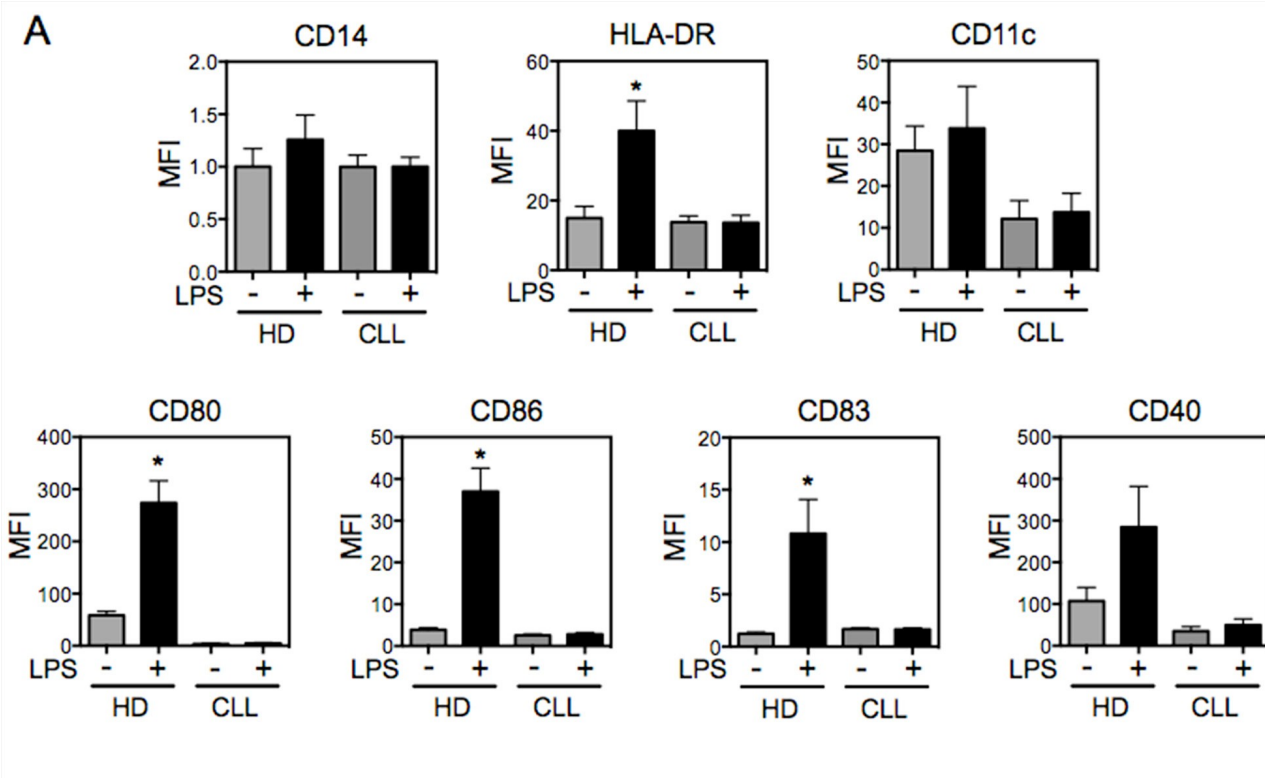


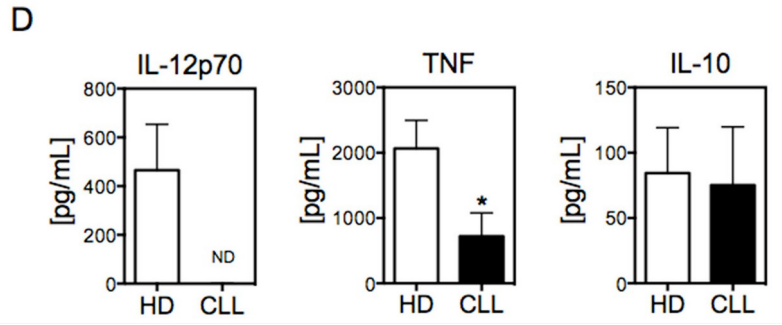






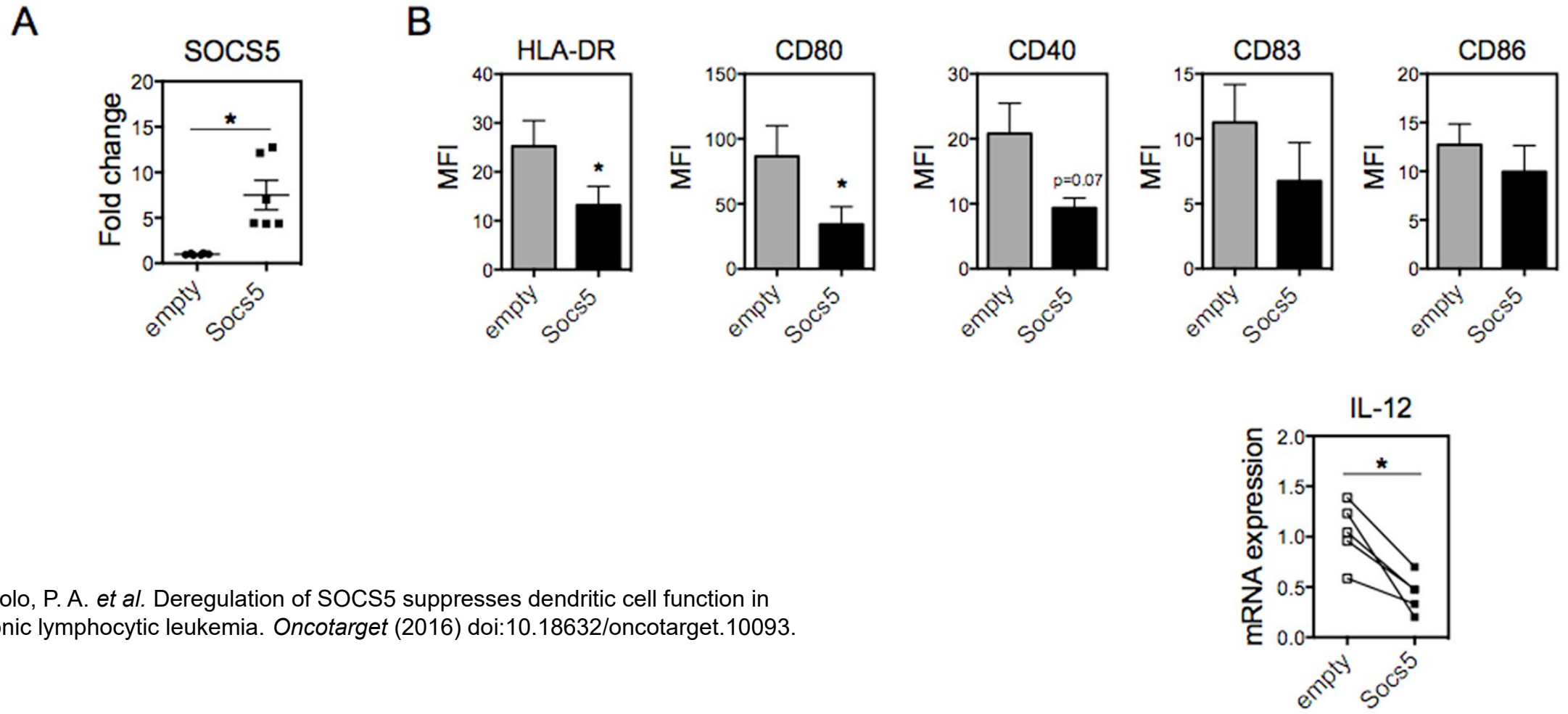
Monocyte differentiation bias is also present in CLL





Toniolo, P. A. *et al.* Deregulation of SOCS5 suppresses dendritic cell function in chronic lymphocytic leukemia. *Oncotarget* (2016) doi:10.18632/oncotarget.10093.

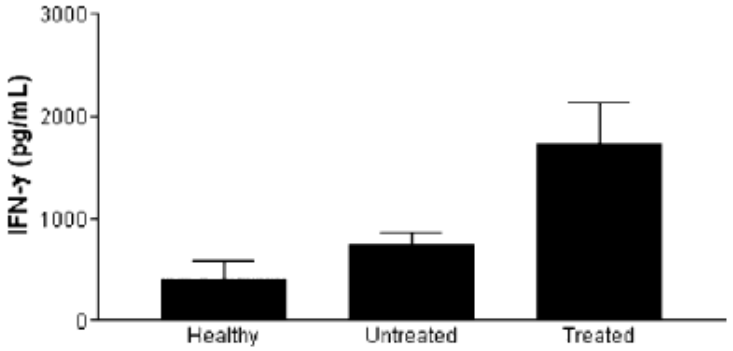
SOCS5-transfected cells do not differentiate into “normal” mo-DC



Toniolo, P. A. *et al.* Deregulation of SOCS5 suppresses dendritic cell function in chronic lymphocytic leukemia. *Oncotarget* (2016) doi:10.18632/oncotarget.10093.

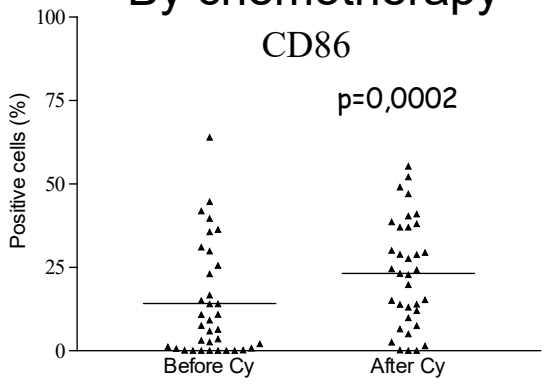
mo-DC bias in cancer is reversed by therapy

By immunotherapy



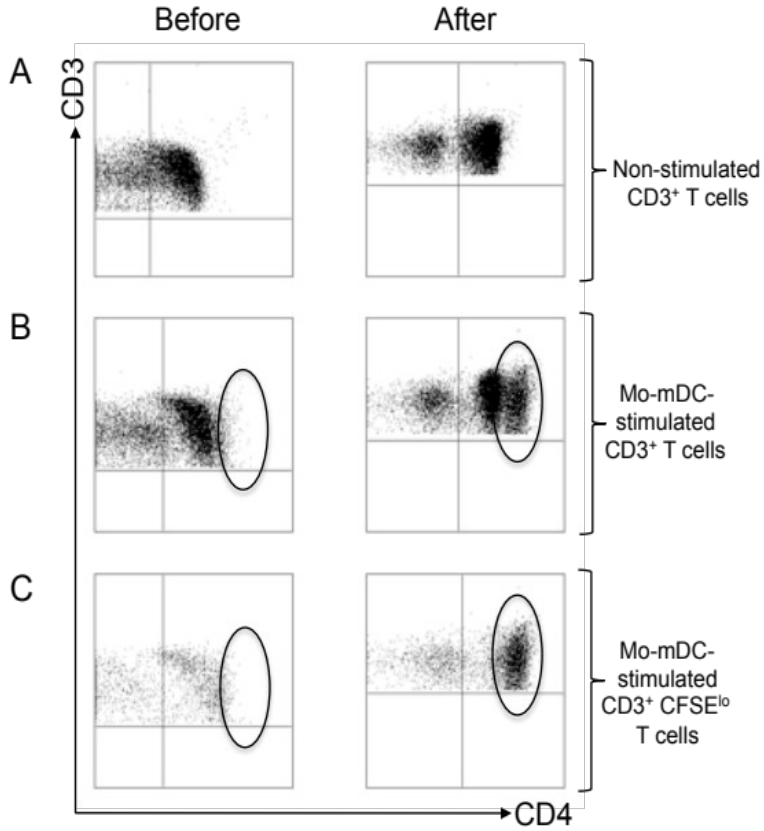
Neves AR, Ensina LFC, Anselmo LB, Leite KRM, Buzaid AC, et al. 2005. *Cancer Immunol. Immunother.* 54(1):61–66

By chemotherapy



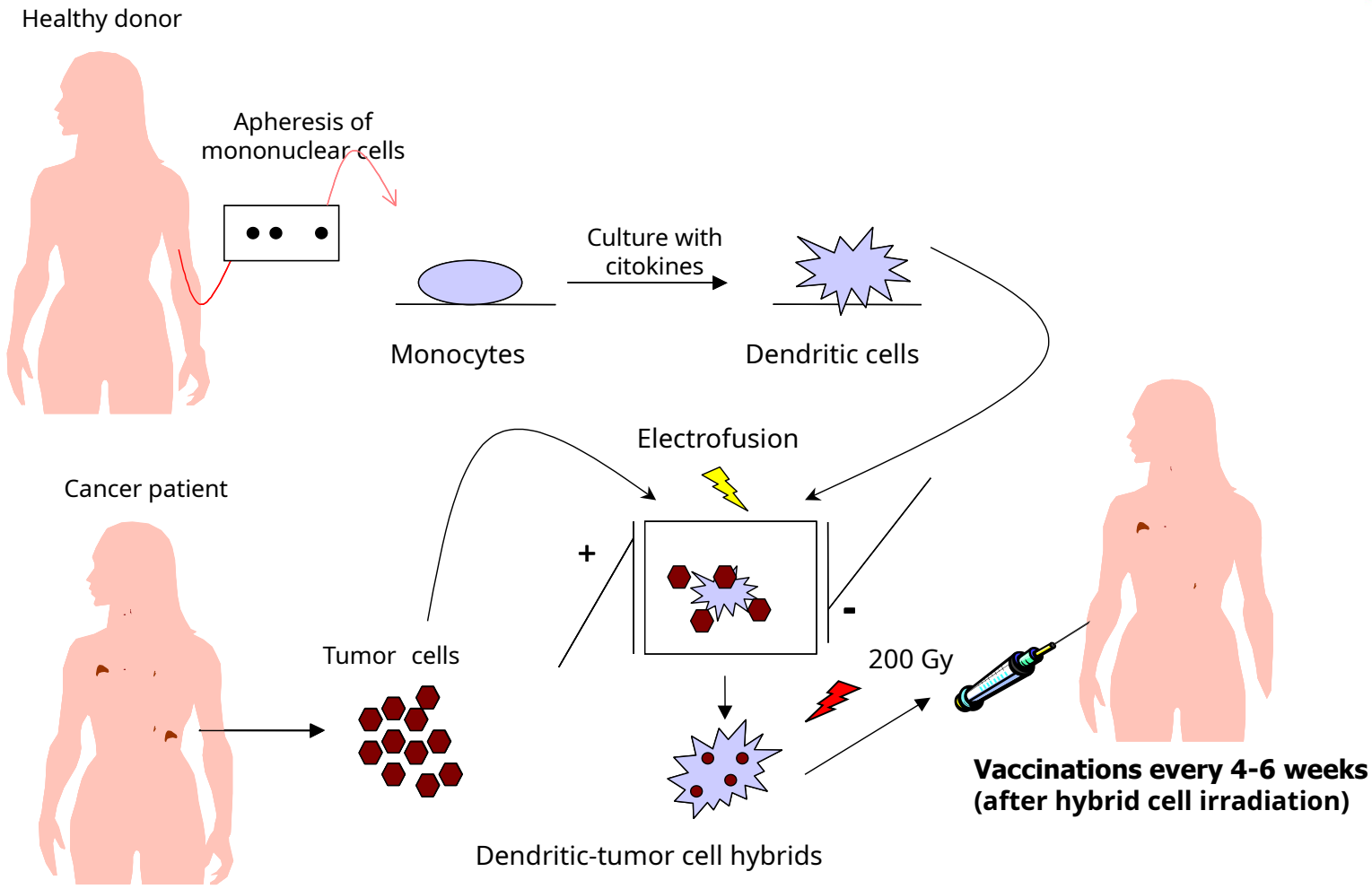
Cavalcanti et al, unpublishded

By surgery



Clavijo-Salomon MA, Crippa A, Pizzo CR, Bergami-Santos PC, Barbuto JAM. 2015. *Cancer Immunol. Immunother.* 64(2):161–71

An alternative strategy to a mo-DC-based vaccination



Barbuto JAM, Ensina LFC, Neves AR, Bergami-Santos PC, Leite KRM, et al. 2004. *Cancer Immunol. Immunother.* 53(12):1111–18

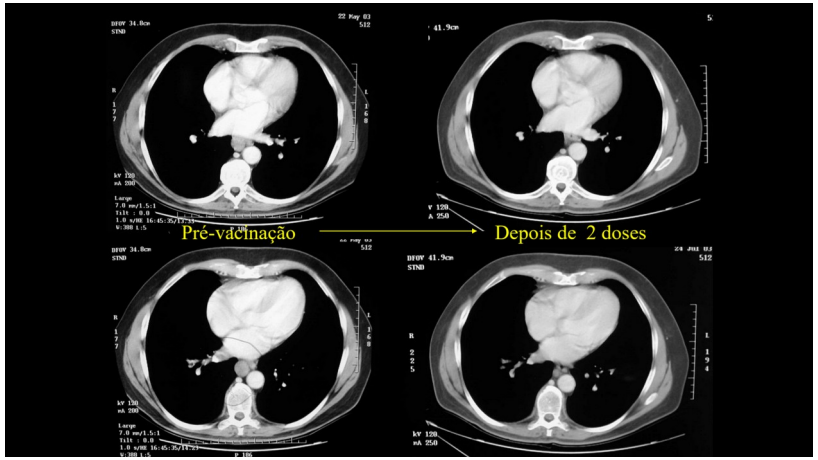
Cancer Immunol Immunother (2004) 53: 1111–1118
DOI 10.1007/s00262-004-0551-7

ORIGINAL ARTICLE

Jose Alexandre M. Barbuto · Luis F. C. Ensina
Andreia R. Neves · Patrícia C. Bergami-Santos
Katia R. M. Leite · Ricardo Marques · Frederico Costa
Siderleny C. Martins · Luiz H. Camara-Lopes
Antonio C. Buzaid

Dendritic cell–tumor cell hybrid vaccination for metastatic cancer

In melanoma patients



In renal cell carcinoma patients

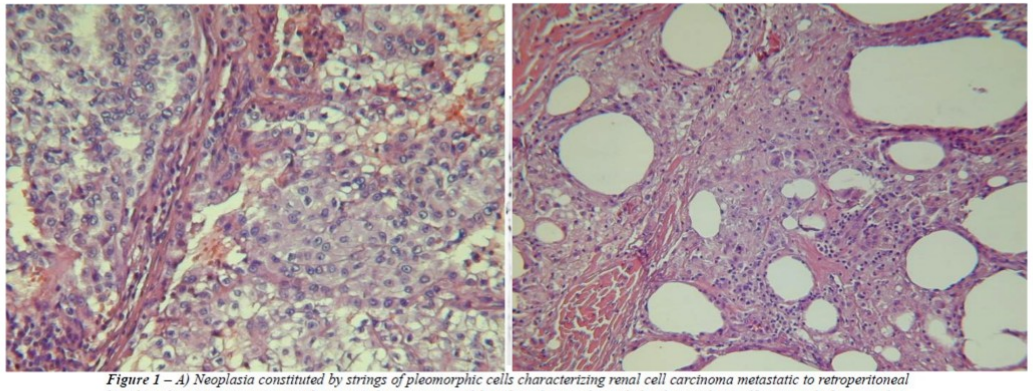


Figure 1 – A) Neoplasia constituted by strings of pleomorphic cells characterizing renal cell carcinoma metastatic to retroperitoneal lymph node. B) Post-treatment. The resected retroperitoneal lymph node reveals epithelioid granuloma, fibrosis and absence of residual tumor.

Case Report
International Braz J Urol
Official Journal of the Brazilian Society of Urology
Vol. 29 (6): 517-519, November - December, 2003

COMPLETE RESPONSE OF METASTATIC RENAL CANCER WITH DENDRITIC CELL VACCINE

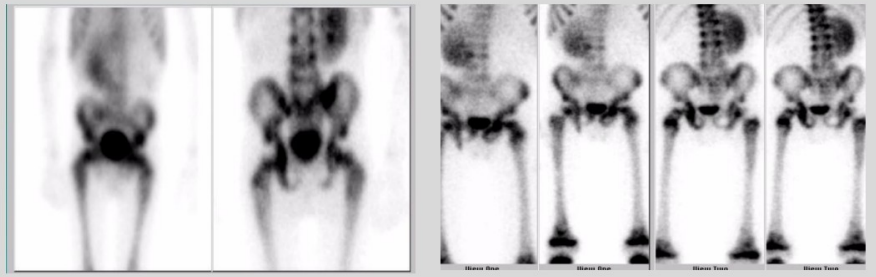
MARCOS DALL'OGLIO, MIGUEL SROUGI, JOSÉ A.M. BARBUTO

Discipline of Urology, Paulista School of Medicine, Federal University of São Paulo, UNIFESP, Sírio Libanês Hospital of São Paulo and Department of Immunology, ICB-USP, São Paulo, SP, Brazil

In neuroblastoma patients

Pré-vacinação

Pós-vacinação



LDH >2000

LDH < 500

Response of advanced refractory neuroblastoma to dendritic-tumor cell hybrid vaccination

Cancers **2023**, *15*, 1239. https://doi.org/10.3390/cancers15041239

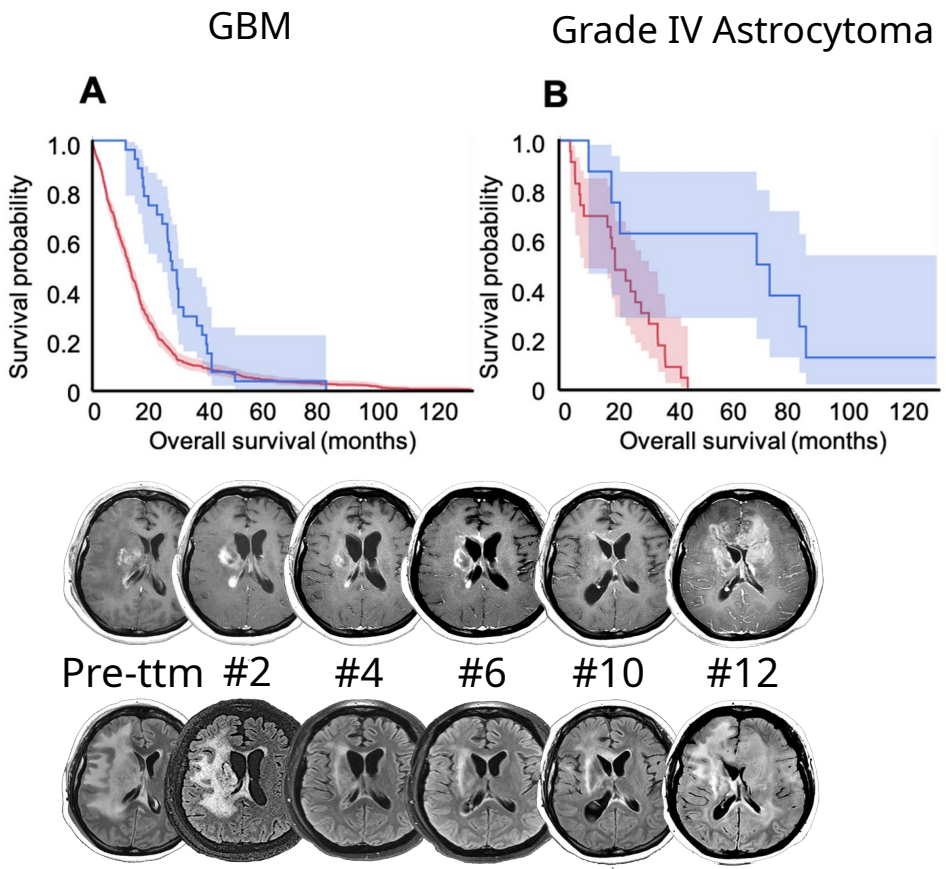
cancers

MDPI

Article

Adjuvant Vaccination with Allogenic Dendritic Cells Significantly Prolongs Overall Survival in High-Grade Gliomas: Results of a Phase II Trial

Guilherme Lepski [1,2], Patricia C. Bergami-Santos [3], Mariana P. Pinho [3], Nadia E. Chauca-Torres [3], Gabriela C. M. Evangelista [3], Sarah F. Teixeira [3], Elizabeth Flatow [3], Jaqueline V. de Oliveira [3], Carla Fogolin [3], Nataly Peres [4], Analía Arévalo [1], Venâncio A. F. Alves [5] and José A. M. Barbuto [3,6,*]



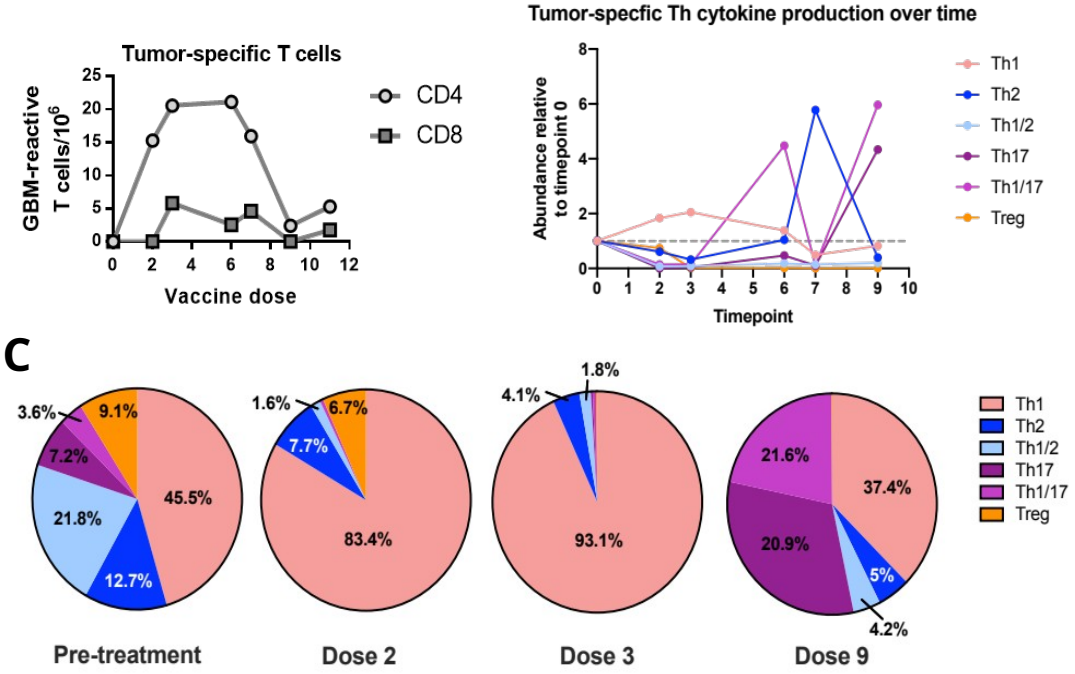
International Journal of *Molecular Sciences*

MDPI

Case Report

Near-Complete Remission of Glioblastoma in a Patient Treated with an Allogenic Dendritic Cell-Based Vaccine: The Role of Tumor-Specific CD4+T-Cell Cytokine Secretion Pattern in Predicting Response and Recurrence

Mariana P. Pinho [1,†], Guilherme A. Lepski [2,3,†], Roberta Rehder [4], Nadia E. Chauca-Torres [1], Gabriela C. M. Evangelista [1], Sarah F. Teixeira [1], Elizabeth A. Flatow [1], Jaqueline V. de Oliveira [1], Carla S. Fogolin [1], Nataly Peres [1,5], Analía Arévalo [2], Venâncio Alves [6], José A. M. Barbuto [1,7,*] and Patricia C. Bergami-Santos [1,*]



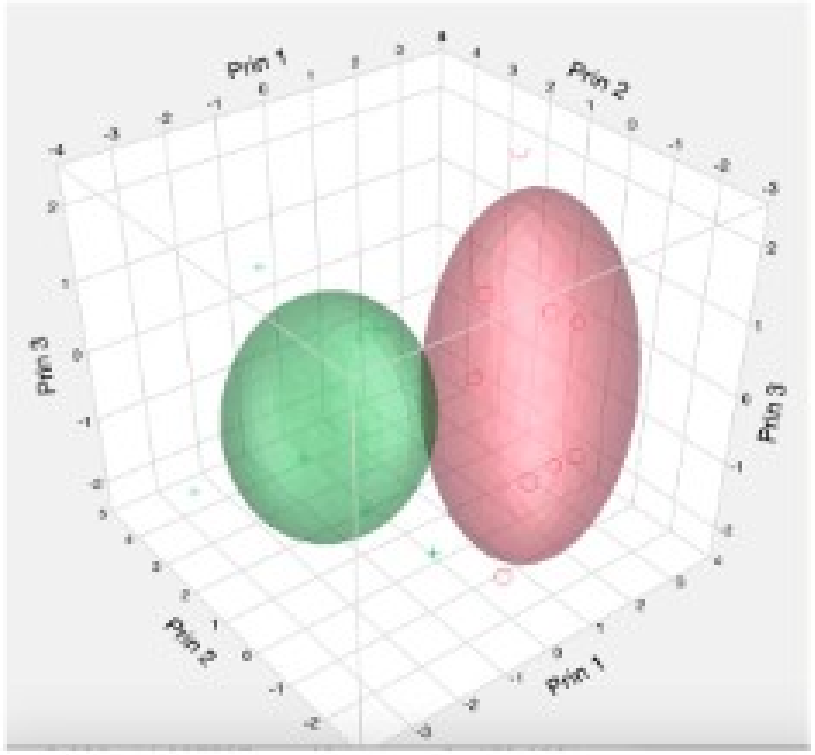
Int. J. Mol. Sci. 2022, 23, 5396. https://doi.org/10.3390/ijms23105396

Article

Profiling of Tumor-Infiltrating Immune Cells and Their Impact on Survival in Glioblastoma Patients Undergoing Immunotherapy with Dendritic Cells

Nataly Peres [1], Guilherme A. Lepski [2,3,*], Carla S. Fogolin [4,5], Gabriela C. M. Evangelista [4,5], Elizabeth A. Flatow [4,5], Jaqueline V. de Oliveira [4,5], Mariana P. Pinho [4], Patricia C. Bergami-Santos [4] and José A. M. Barbuto [4,5]

A



	Cluster 1		Cluster 2	
	mean	SD	mean	SD
Overall Survival	55.2	38.9	19.1	6.6
Survival since 1st recurrence	26.5	19.4	4.0	2.4
Survival since vaccination	17.5	18.4	1.9	1.3
HLA-DR	39.2	30.0	53.9	32.2
PD-L1	13.4	14.4	7.4	5.0
CD86	7.0	10.9	26.7	26.2
CD45	13.4	11.0	12.8	10.1
HLA-DR/CD45	67.2	25.6	79.4	22.3
CD45/PD-L1	35.7	21.2	17.4	10.5
CD45+/CD86+	18.7	27.7	39.1	35.9
CD45+/CD11b+/CD14+/HLADR+	96.8	3.9	94.1	7.8
CD45+/CD11b+/CD14+/PD-L1+	59.4	25.7	30.6	15.0
CD45+/CD11b+/CD14+/CD86+	25.4	20.1	55.7	31.3
Age	41	11	50	13
KPS	89	12	57	12
ECOG	0	1	2	0

Peres, N. *et al.* Profiling of Tumor-Infiltrating Immune Cells and Their Impact on Survival in Glioblastoma Patients Undergoing Immunotherapy with Dendritic Cells. *Int J Mol Sci* **25**, (2024).

PROCEEDINGS OF THE ROYAL SOCIETY OF MEDICINE

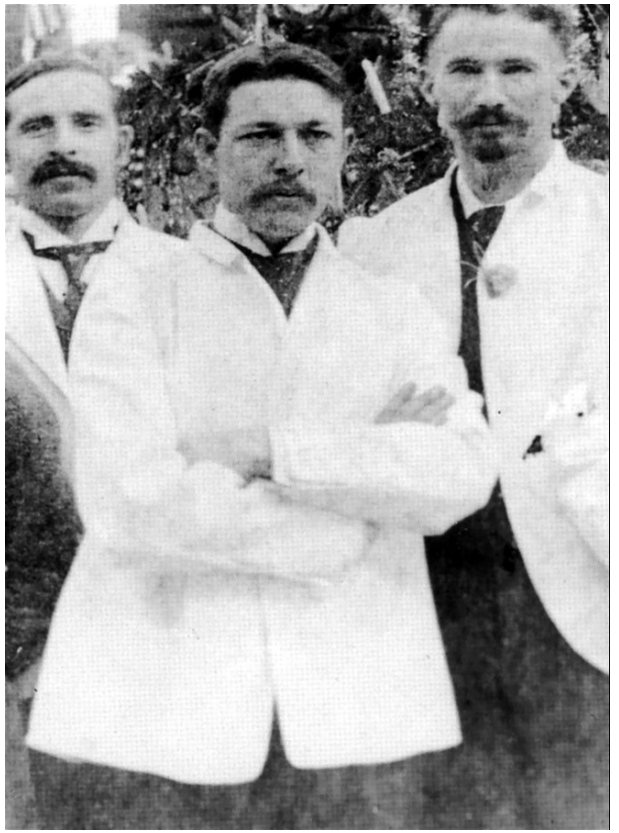
Surgical Section.

July 13, 1909.

Mr. J. Warrington Haward, President of the Section, in the Chair.

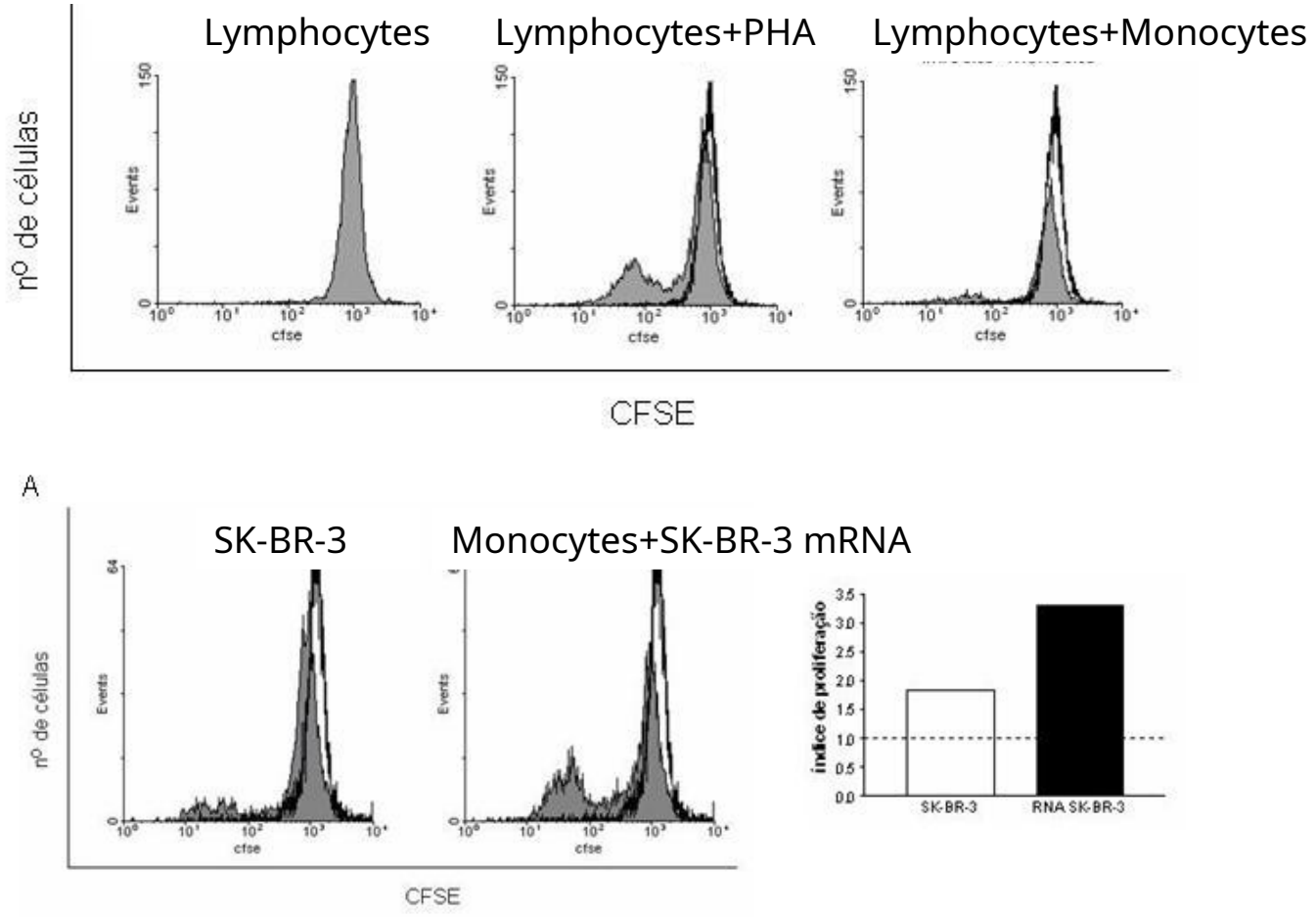
The Treatment of Inoperable Sarcoma by Bacterial Toxins (the Mixed Toxins of the Streptococcus erysipelas and the Bacillus prodigiosus).

By William B. Coley, M.D. (New York.)[1]



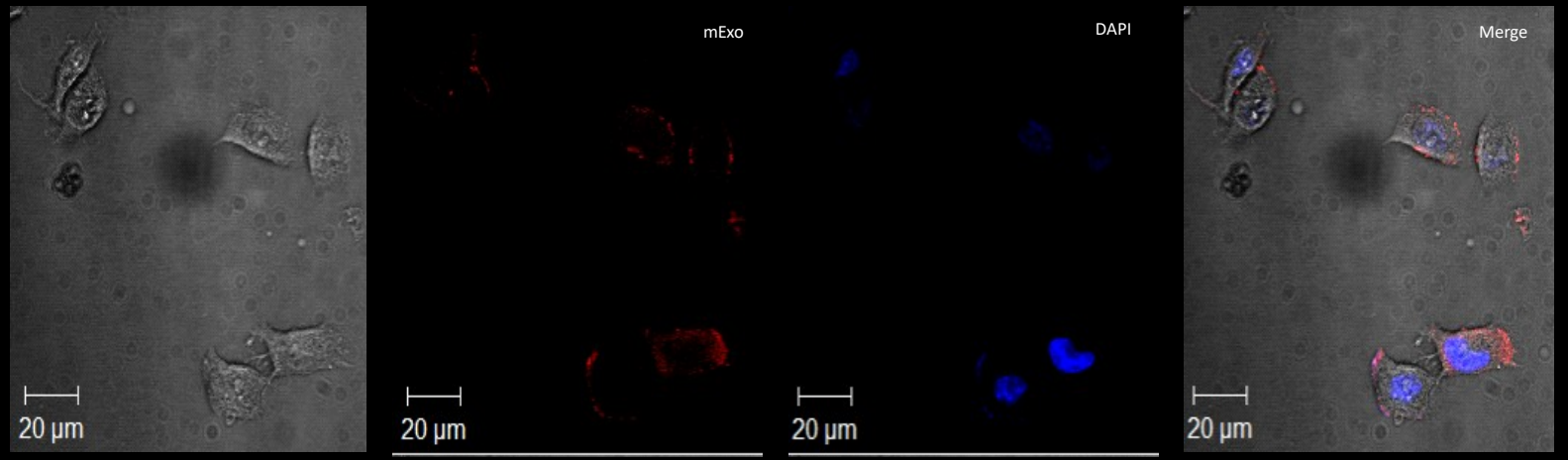
THE subject upon which I have been asked to address you is one upon which I have been working constantly the last seventeen years, and one which has grown more interesting to me with each succeeding year. While the results have not been as satisfactory as one who is seeking perfection could wish, they have been sufficiently real and tangible, I think, to be entitled to more careful consideration than they have yet received. Furthermore, they may have an important bearing upon the whole cancer problem, since, if by the administration of certain bacterial toxins we can cause the degeneration, death, and absorption of living tumour cells of one variety of cancer -sarcoma- it is not unreasonable to suppose that by the use of some other forms of bacterial toxins we may succeed in destroying or inhibiting the growth of the other and more common variety -carcinoma.

Tumor mRNA-transfected cells: Targets for lymphocyte responses



Menezes et al., ICI - 2007.

Dendritic Cell-Derived Exosomes may be a Tool for Cancer Immunotherapy by Converting Tumor Cells into Immunogenic Targets



Romagnoli, G. G., Zelante, B. B., Toniolo, P. A., Migliori, I. K. & Barbuto, J. A. M. Dendritic Cell-Derived Exosomes may be a Tool for Cancer Immunotherapy by Converting Tumor Cells into Immunogenic Targets. *Frontiers in immunology* 5, 692 (2014).

To deal with cancer we need a

TEAM

Tumor **E**nvironment **A**ctive **M**odulation

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Two possible postures in Science:

