Immune dysfunction in ovarian carcinoma and implications for immunotherapy

Vassili SOUMELIS, MD, PhD
Professor of immunology
Hôpital St Louis, Paris

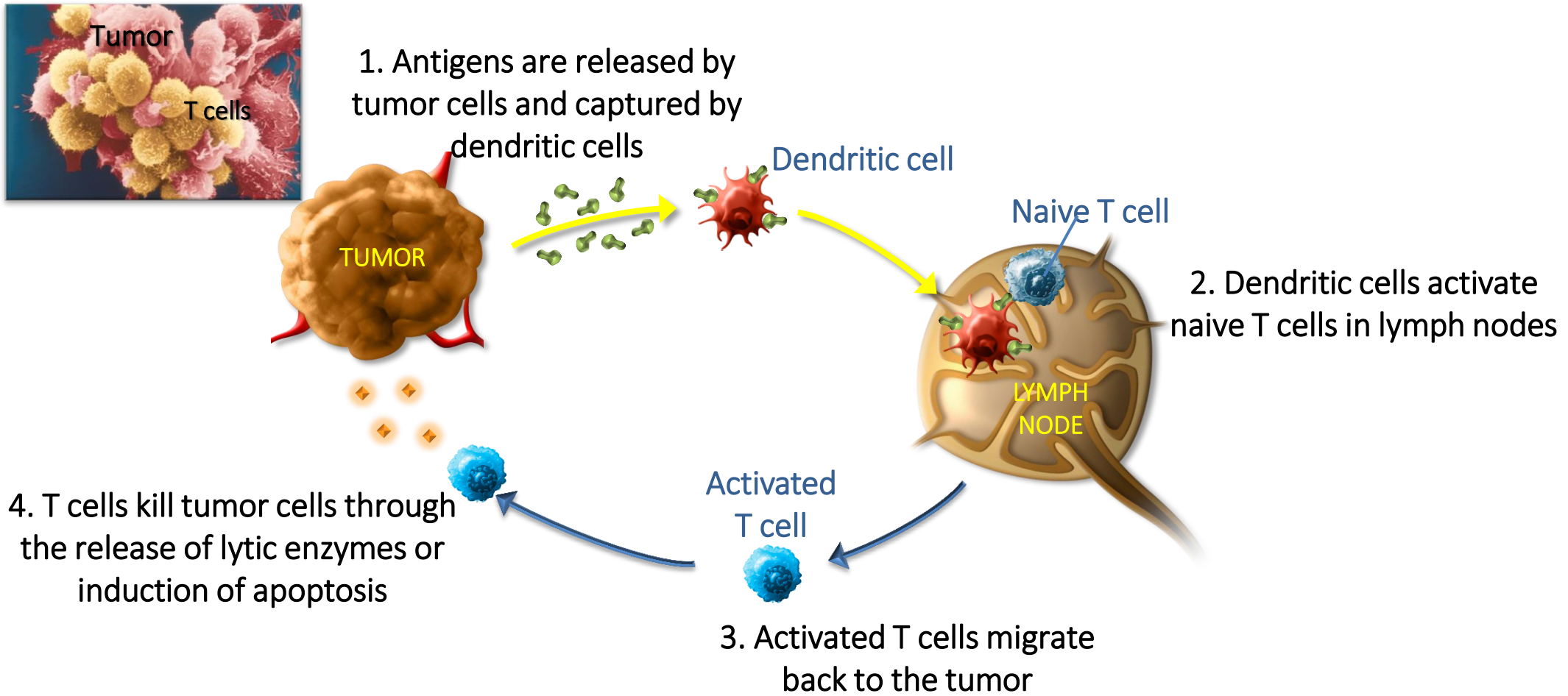
Team leader
Institut Curie, Paris

Séminaire de restitution des projets financés par le programme PAIR GYNECO
La Rochelle, 23 novembre 2018

Equipes partenaires

- **Equipe 1: V Soumelis/S Amigorena, Inserm U932, Curie**
- **Equipe 2: C Caux/N Bendriss-Vermare/Ray-Coquard, CRCL U-1052/ CLB**
- **Equipe 3: F. Penault-Llorca/ C Pomel, Centre Jean Perrin**
- **Equipe 4: L Zitvogel, IGR**

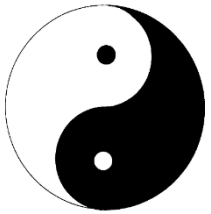
Main steps to induce anti-tumor immunity



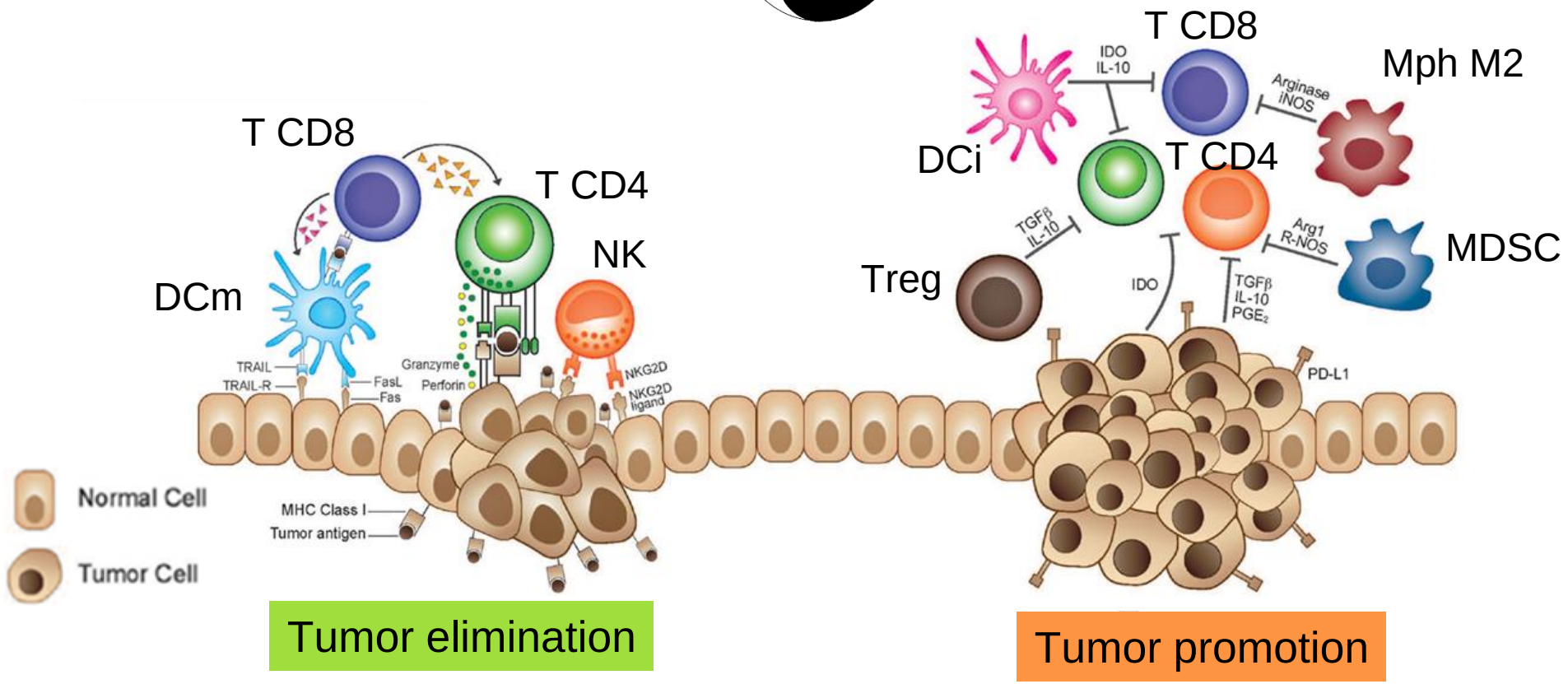
May KF Jr et al. In: Prendergast GC et al. *Cancer Immunotherapy*. 2nd ed. Elsevier; 2013:101–113.

The ambivalent role of the immune system in cancer

Anti-tumor response (immunosurveillance)



Pro-tumor response (immune escape)

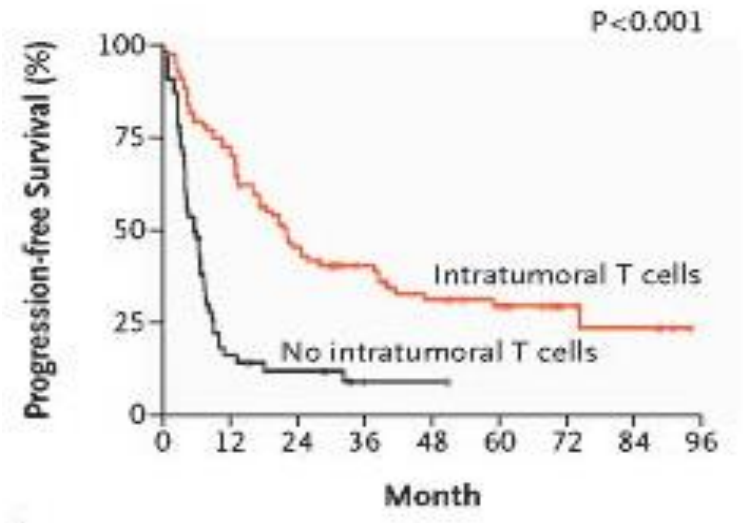


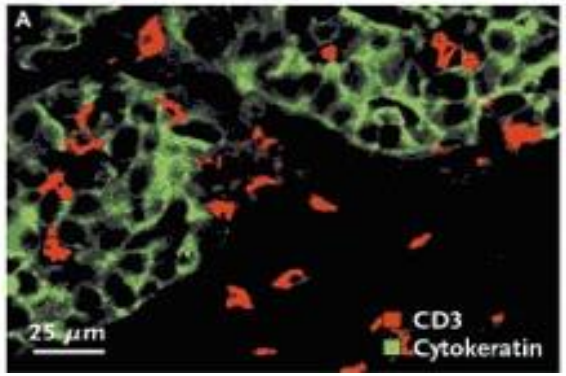
Tumor elimination

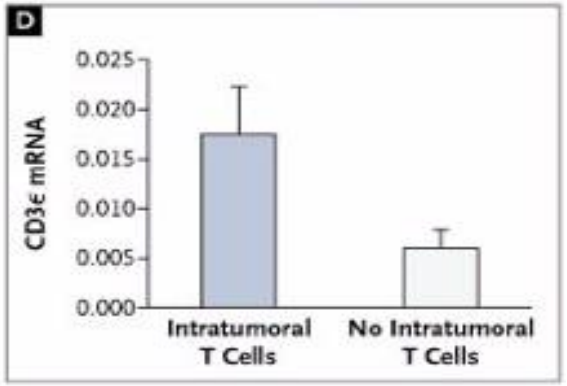
Tumor promotion

Evidence of tumor immunosurveillance in ovarian cancer

Tumor-infiltrating lymphocytes Correlation with survival in ovarian cancer patients

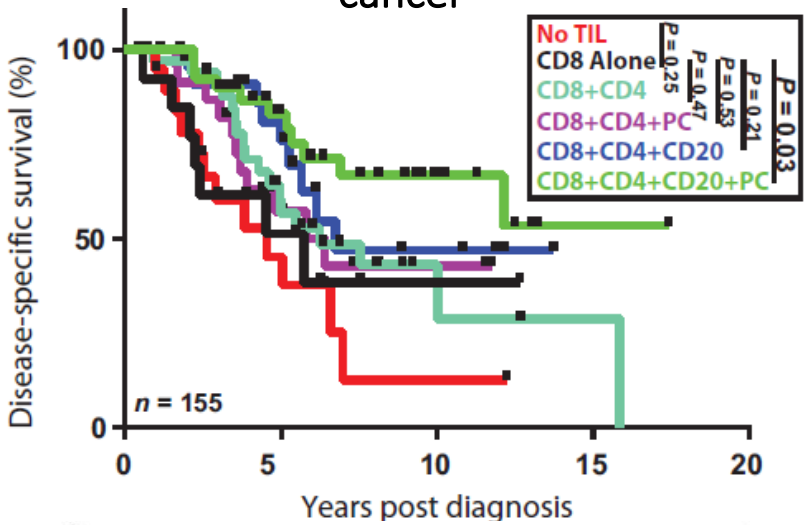


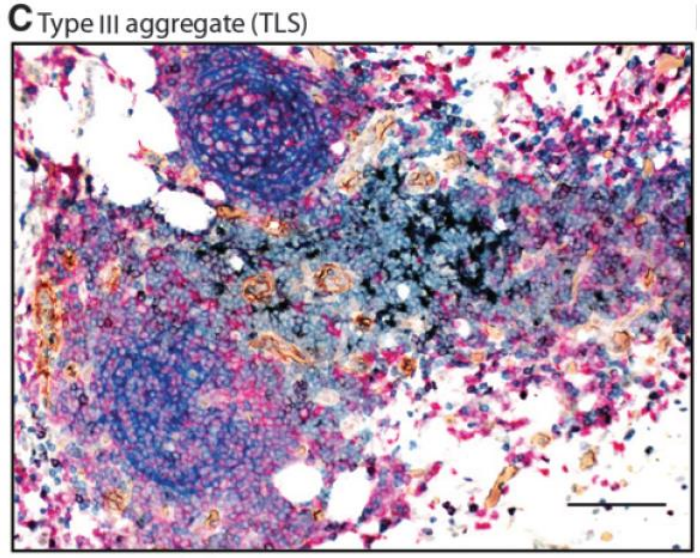




Zhang et al. NEJM 348:203, 2003

Tumor-infiltrating plasma cells are associated with Tertiary Lymphoid Structures, cytotoxic T cell responses and superior prognosis in ovarian cancer





CD3/Tcell
CD8/CTL
CD20/Bcell
CD21/FDC
CD208/DC
PNAd/HEV

Kroeger et al. Clin Cancer Res 2016

META-ANALYSIS OF 10 STUDIES COMPRISING 1815 PATIENTS WITH OVARIAN CANCER

Intraepithelial TILs are a robust predictor of outcome in ovarian cancer and define a specific class of patients

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Zhang(2003)	0.61	0.18	12.5%	1.84 [1.29, 2.62]
Sato(2005)	1.11	0.307	8.8%	3.03 [1.66, 5.54]
Hamanishi(2007)	2.031	0.518	4.8%	7.62 [2.76, 21.04]
Callahan(2008)	0.548	0.222	11.2%	1.73 [1.12, 2.67]
Han(2008)	0.563	0.258	10.1%	1.76 [1.06, 2.91]
Tomsova(2008)	1.308	0.296	9.1%	3.70 [2.07, 6.61]
Adams(2009)	0.694	0.315	8.6%	2.00 [1.08, 3.71]
Clarke(2009)	0.282	0.106	14.5%	1.33 [1.08, 1.63]
Leffers(2009)	1.02	0.251	10.3%	2.77 [1.70, 4.54]
Stumpf(2009)	0.895	0.258	10.1%	2.45 [1.48, 4.06]
Total (95% CI)			**100.0%**	**2.24 [1.71, 2.92]**

Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 29.38$, $df = 9$ ($P = 0.0006$); $I^2 = 69\%$

Test for overall effect: $Z = 5.92$ ($P < 0.00001$)

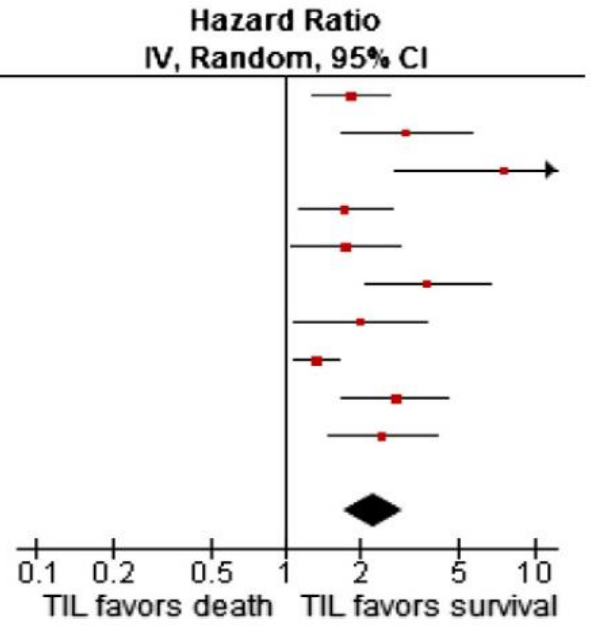
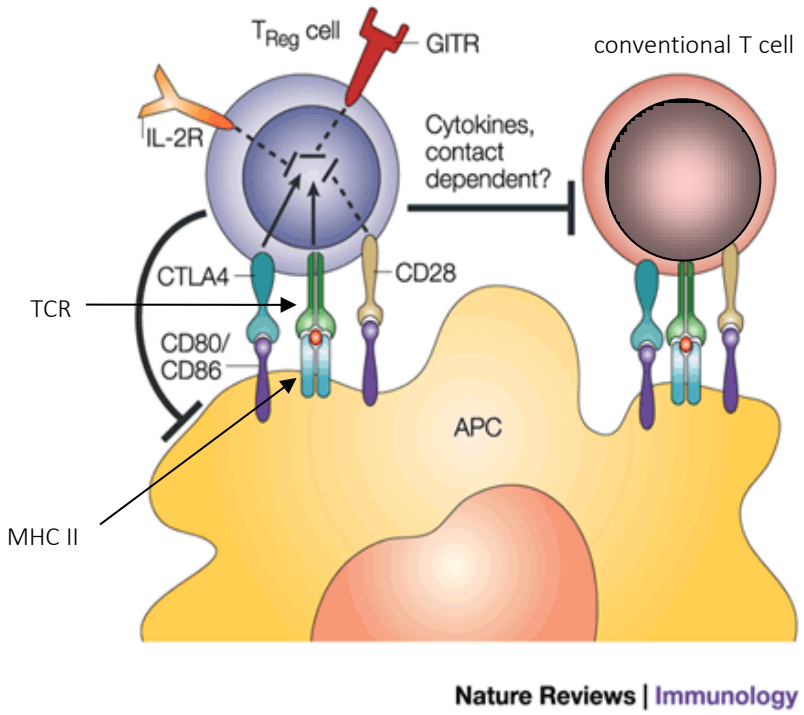


Fig. 2. Forest plot of associations of TILs with overall survival in select studies.

Hwang WT, Adams SF, Tahirovic E, Hagemann IS, Coukos G. Prognostic significance of tumor-infiltrating T cells in ovarian cancer: a meta-analysis. Gynecol Oncol. 2012;124(2):192-8.

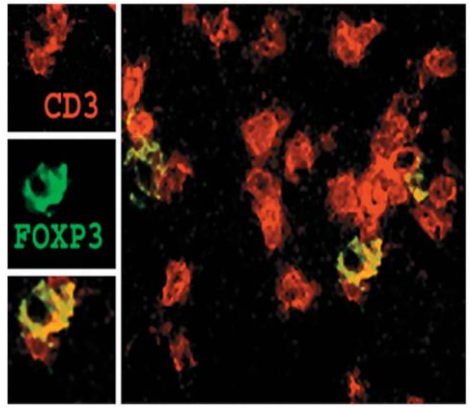
Immune evasion in ovarian cancer through recruitment of immunosuppressive cells

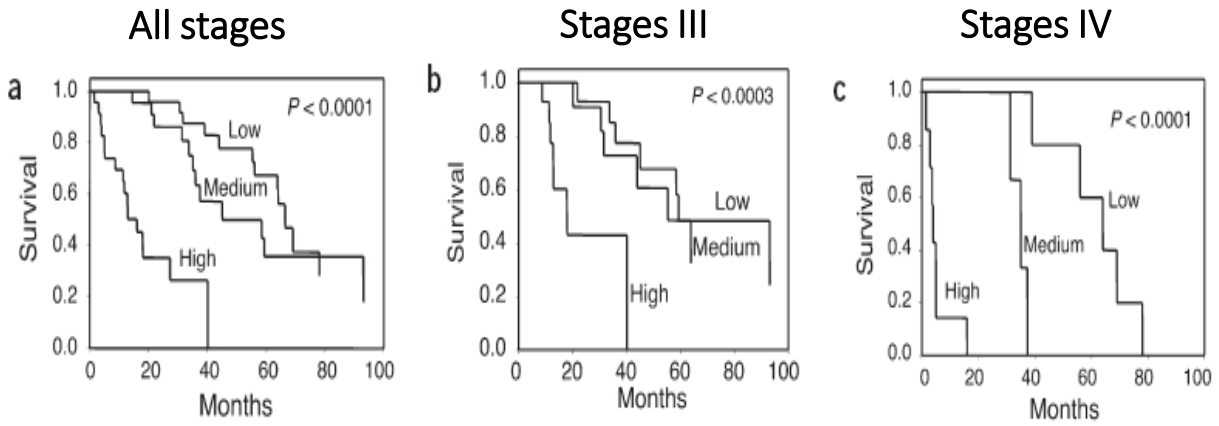
Regulatory T lymphocytes (Treg) inhibit conventional T cell activation



Adapté de : Wood, K.J. and Sakaguchi, S. (2003) *Nat Rev Immunol* **3**, 199-210

Regulatory T cell (Treg) Infiltration Is a Bad Prognosis Factor in Ovarian Tumor



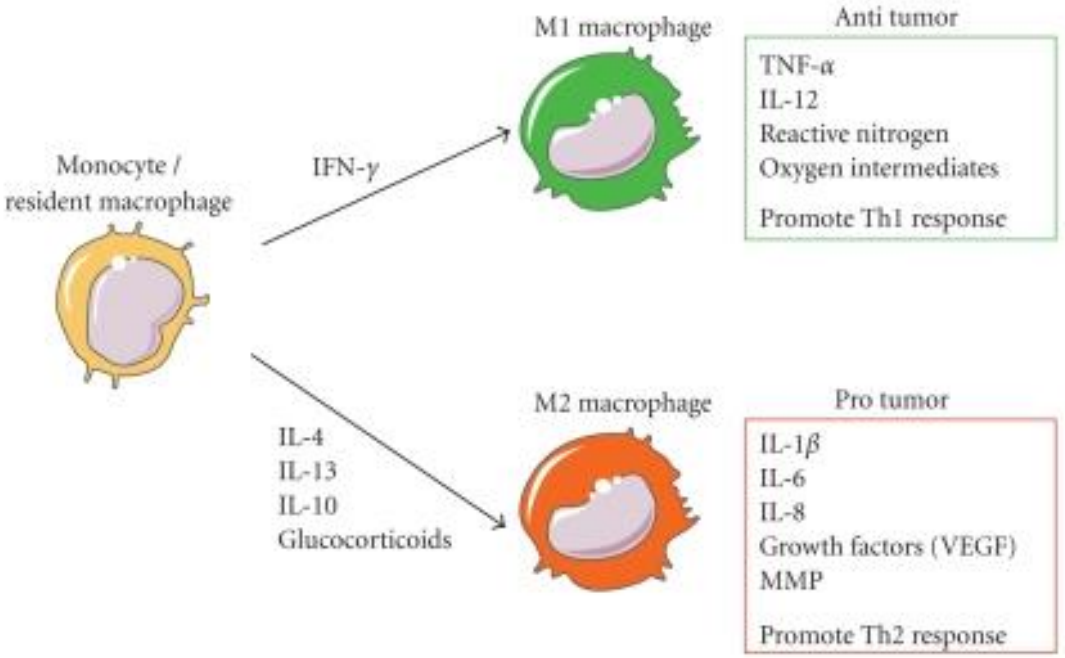


- Increased Treg frequency in blood of patients suffering from different cancer types (Udaya 2002, Wolf 2003)

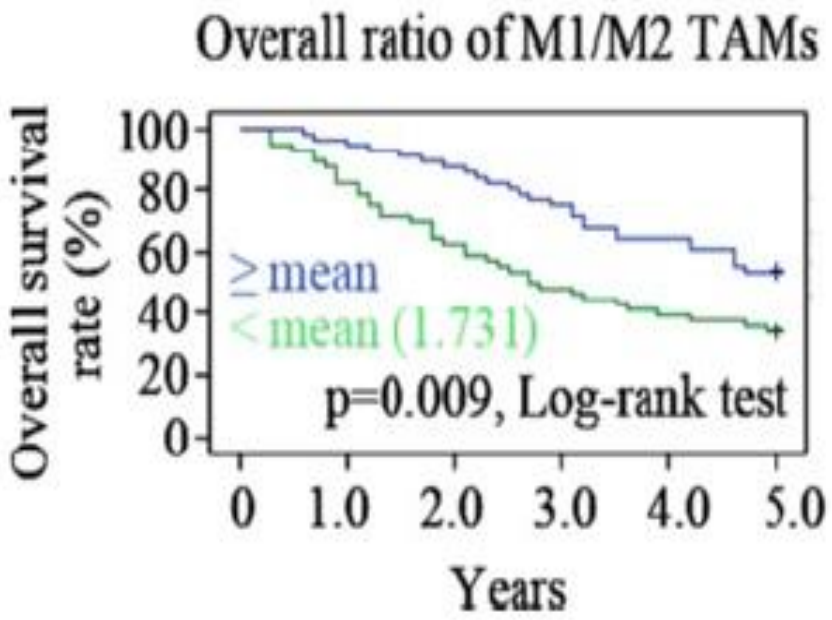
Curiel. *Nat Med*. 2004;10:942.

Immune evasion in ovarian cancer through recruitment of immunosuppressive cells

Dichotomy between M1/M2 phenotypes



A high M1/M2 ratio of tumor-associated macrophages is associated with extended survival in ovarian cancer patients



M1: CD68+INOS+
M2: CD68+CD163+

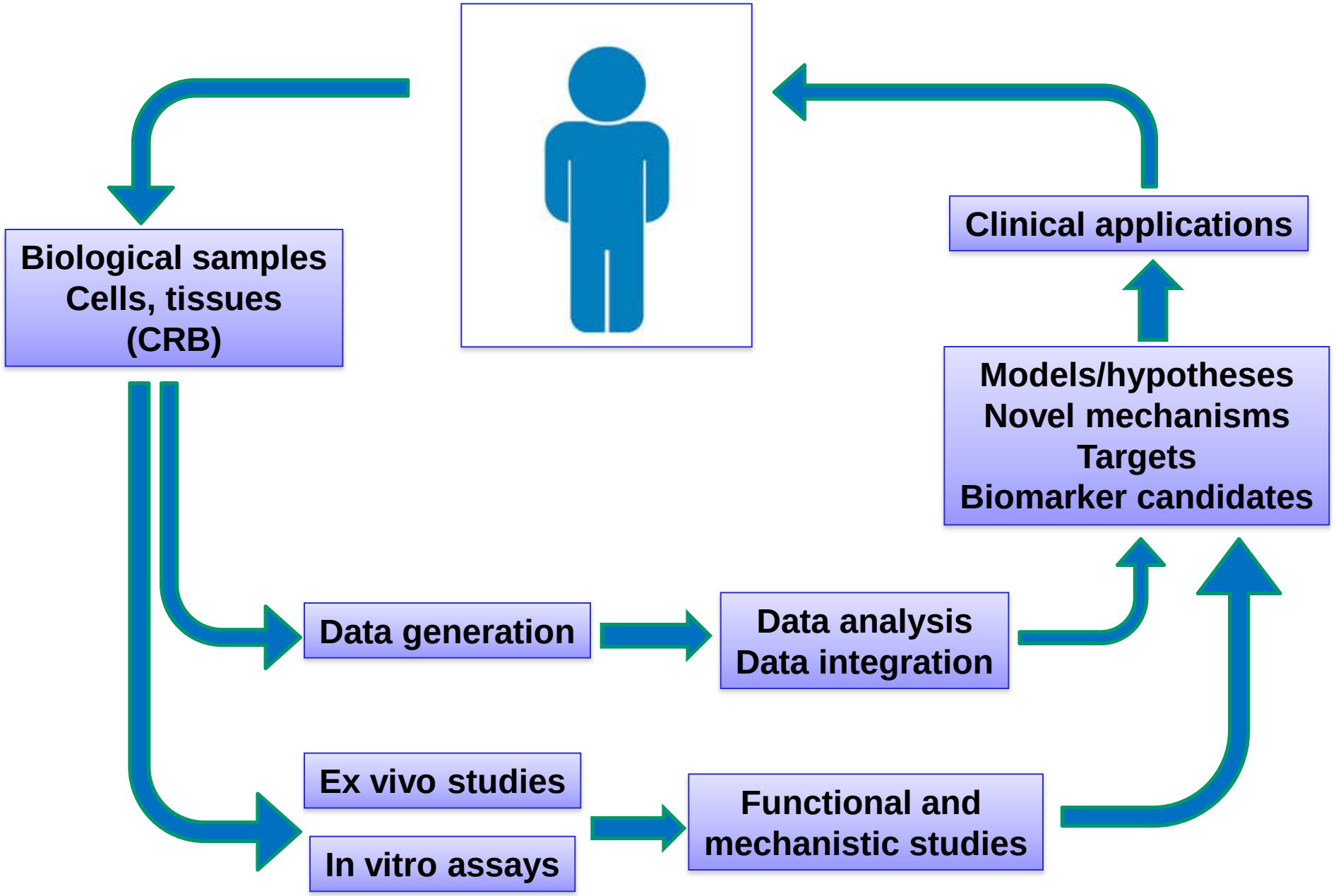
Zhang M, J Ovarian Res. 2014

Hypothesis and objectives
PAIR GYNECO IMMUNO program

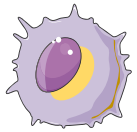
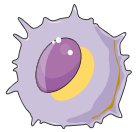
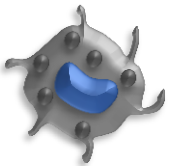
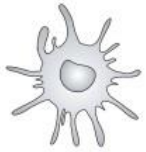
- General hypothesis : characterization and understanding of these mechanisms together with the identification of the tumor and immune determinants that contribute to anti-tumor immunity will allow the development of innovative therapeutic strategies inducing and/or restoring anti-tumor immunity.

- Overall objectives:
  - To identify pathways contributing to immune evasion in OC
  - To discover targets to restore anti-tumor immunity in OC

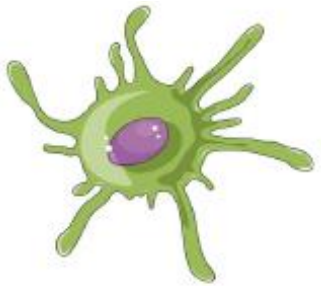
A patient-centric strategy: from the patient and back to the patient



Diversity of human dendritic cell subsets

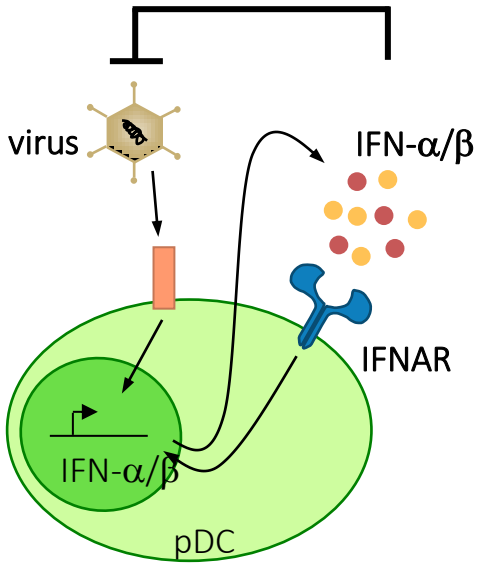
Blood	 BDCA1^{+} DC CD11c^{+} BDCA1^{+} CD11b^{+}	 BDCA3^{high} DC CD11c^{low} BDCA3^{high} CD11b^{-} XCR1^{+} Clec9A^{+}	 Plasmacytoid DC CD11c^{-} BDCA2^{+} CD123^{+}
Tissues	 BDCA1^{+} DC CD11c^{+} BDCA1^{+} CD11b^{+}	 BDCA3^{high} DC CD11c^{low} BDCA3^{high} XCR1^{+} Clec9A^{+}	 Langerhans cells CD11c^{low} CD11b^{-} CD1a^{high} CD207^{+} EpCAM^{high}
Inflammation sites	 Inflammatory DC CD11c^{+} CD11b^{+} SIRPα^{+} FcεR1^{+} BDCA1^{+}	 pDC CD11c^{-} BDCA2^{+} CD123^{+}	

Functional specialization of DC subsets

pDC	BDCA3/CD141$^+$ DC	BDCA1/CD1c$^+$ DC	Inflammatory Mo-DC	Langerhans cells
				
Production of type I and III Interferons	Production of IL-12 and type III interferons	IL-23 production?	Production of TNF, ROI, NOI.	Skin homeostasis?
Th1, Th17 or Treg induction?	Th1 or Treg induction?	Th22, Th17 or Th2 induction?	Th17 or Th2 induction?	Treg induction?
	Cross-presentation of exogenous antigens to CD8$^+$ T cells	Presentation of exogenous antigens to CD4$^+$ T cells		
Innate defenses against viruses	Tolerance to self / Cellular immunity to intracellular pathogens and tumor	Cellular & humoral immunity to extracellular pathogens	Innate defenses against infections	Skin defense against Infections?

Vu Mahn et al. Front Immunol 2015

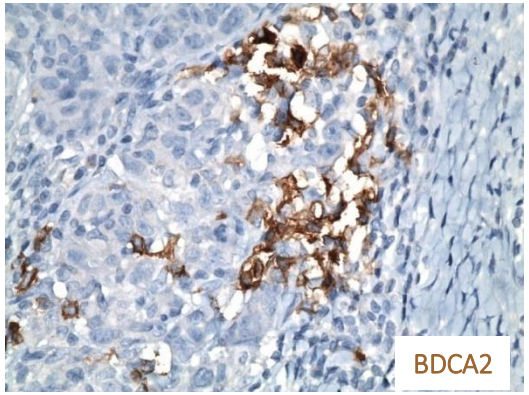
High tumor infiltration by IFNa-deficient plasmacytoid DC is associated to poor clinical outcome

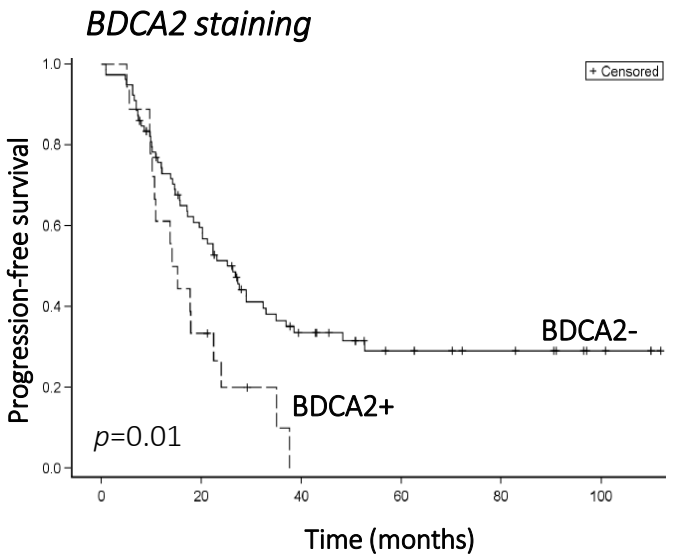


Natural Interferon Producing Cells

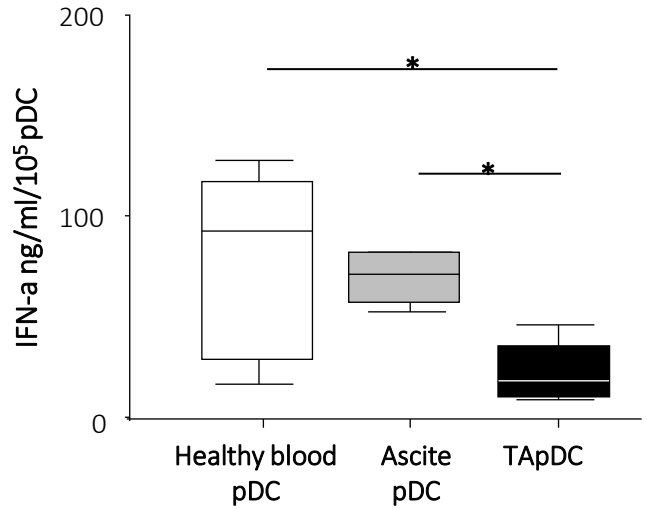
ROLE IN
ANTI-VIRAL DEFENSE

Ovarian cancer





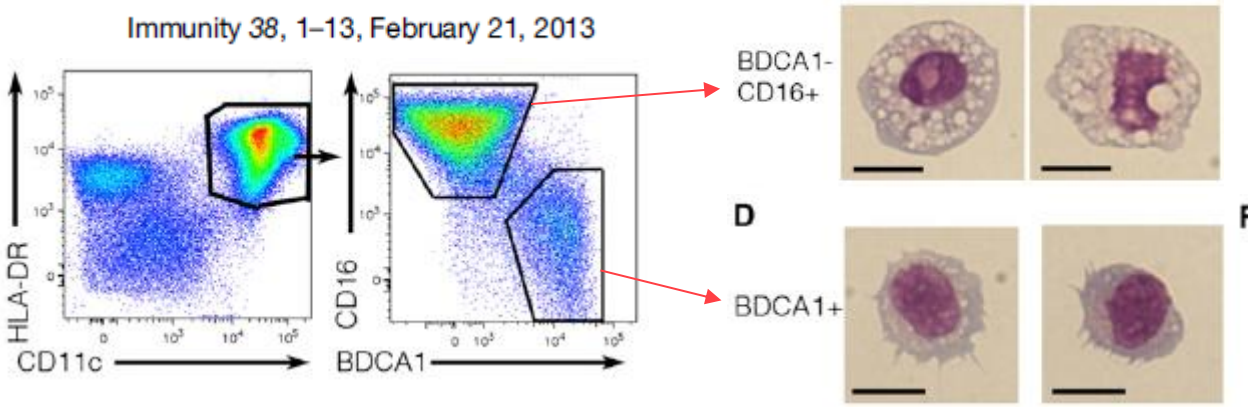
Labidi-Galy et al, OncoImmunol 2012



Labidi-Galy et al, Cancer Res 2011

Human inflammatory dendritic cells induce Th17 cell differentiation

Ovarian cancer ascites

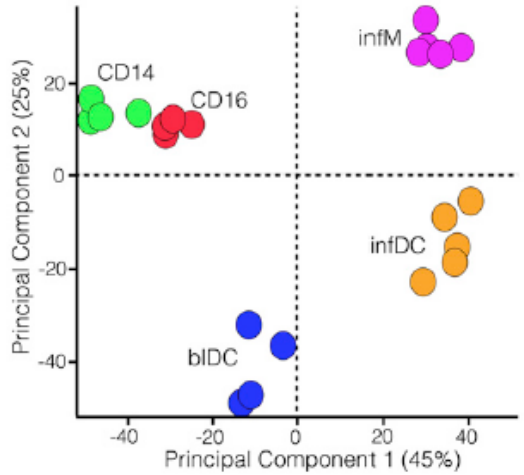


macrophages

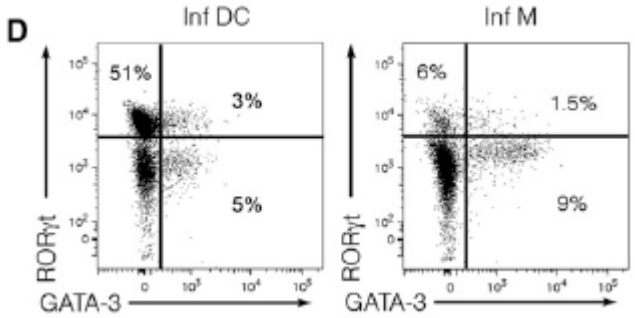
Inflammatory DC
CD14+ FceRI+ Sirpa+

infDC represent a distinct DC subset

(Gene expression profile – microarray Affymetrix)

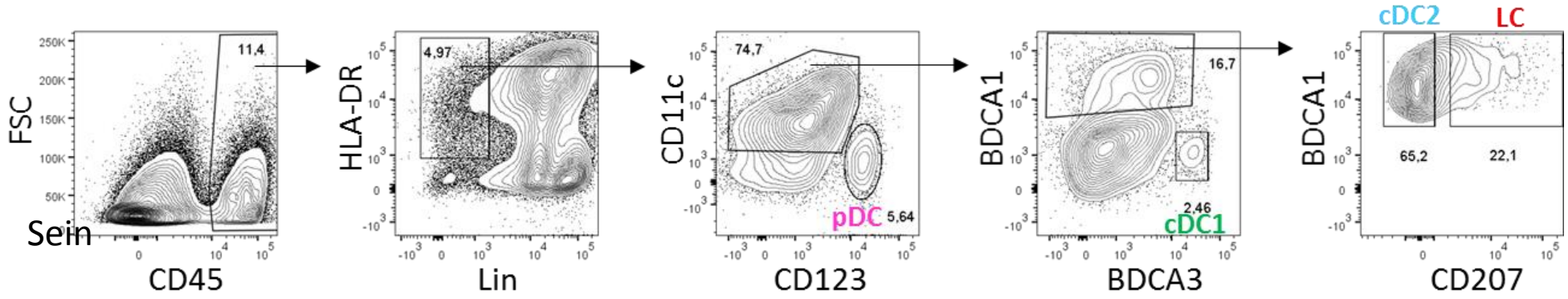


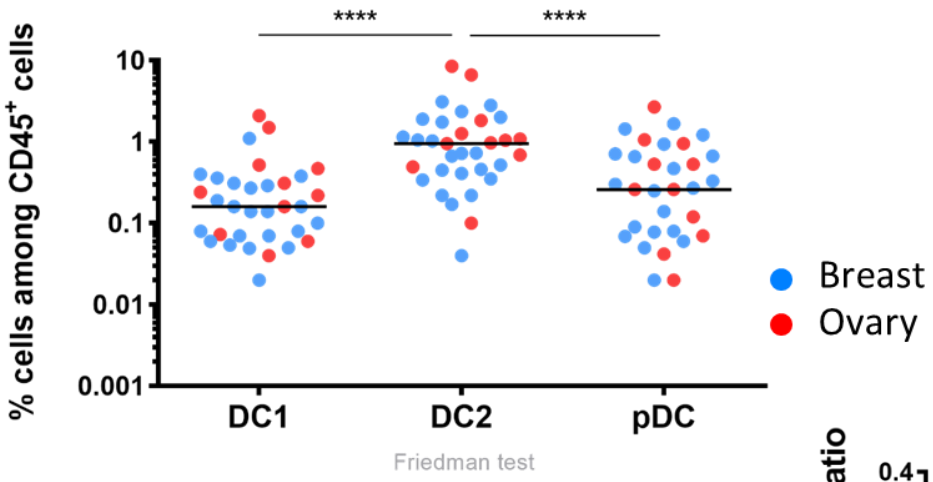
infDC induce Th17 cells

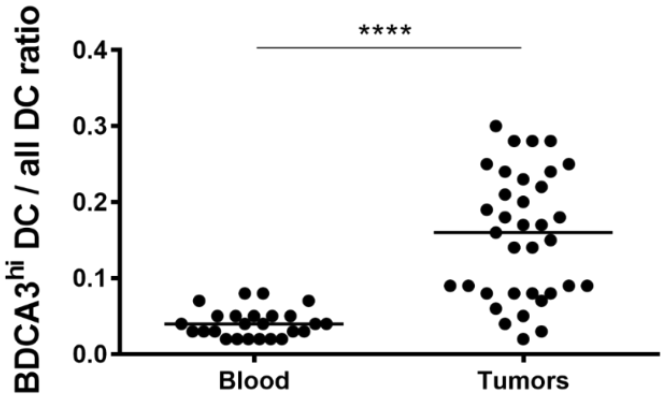


Segura et al, Immunity 2013

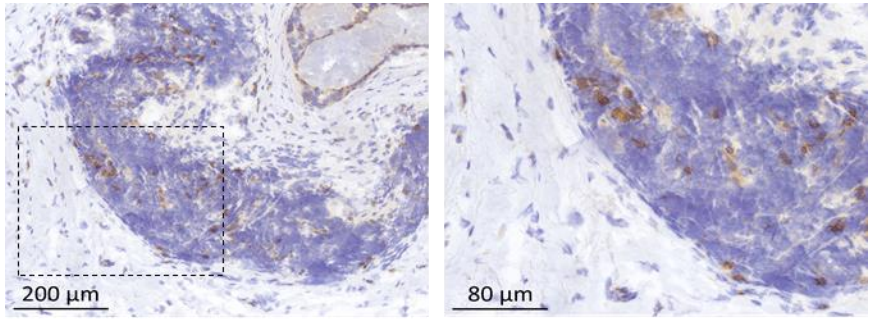
CD141⁺ DC (cDC1) are enriched in ovarian cancer among other DC populations



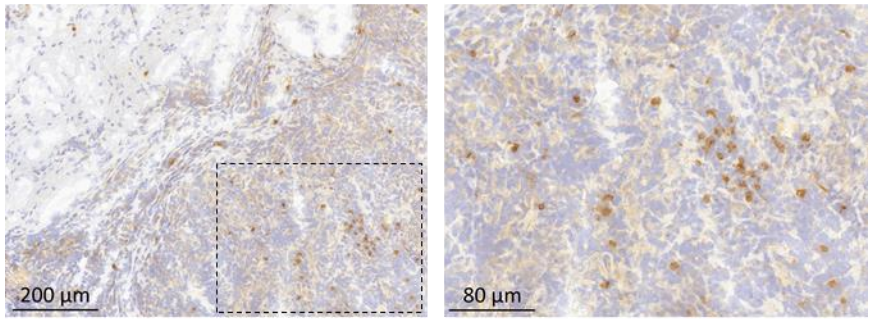




Breast cancer

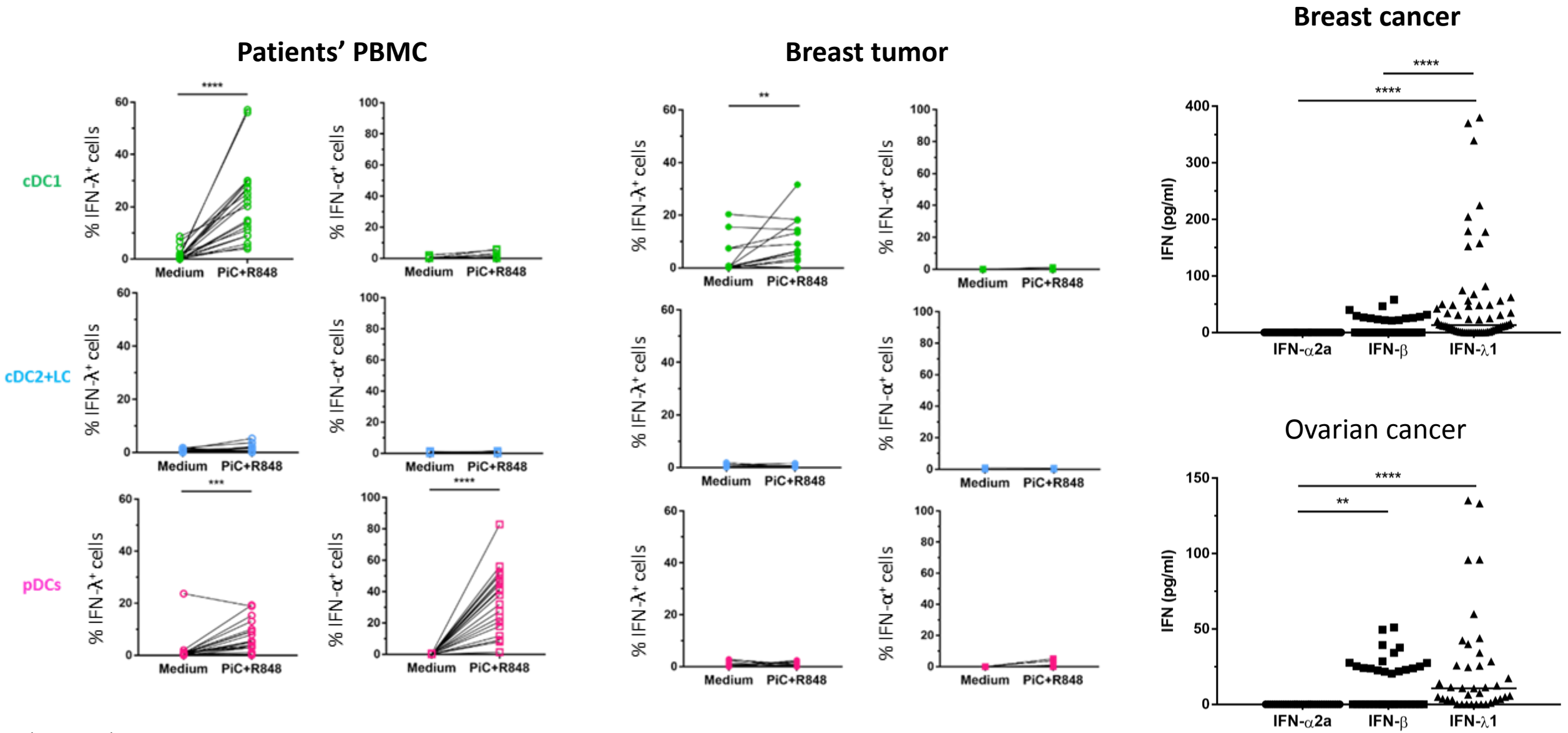


Ovarian cancer



Hubert et al, in revision

In contrast to pDC, cDC1 can be reactivated and produced IFN-L in cancer



Hubert et al, in revision

Definition of tumor inflammation states using large-scale multiprocessing analysis of human primary ovarian cancer and breast tumors

A non-interventional prospective study : 2011 to 2016

Inclusion criteria

FRESH TISSUES

Tumor — **Juxta Tumor**

Breast cancer (BC) or ovarian cancer (OC)

Inclusion criteria:

- All subtypes
- No immune modulation prior to surgery (1 month)

Recruitment: **483 BC patients, + 16 benin tumors**
22 OC patients + 18 kystic lesions

Experiments

A) TME cellular composition

3 Multiparametric Flow cytometry (FACS) panels

- **A:** Neutrophils, fibroblasts, macrophages subsets, epithelial cells, endothelial cells, oxydative stress
- **B:** CD14+DC, MoMac, B cells, T cell subsets, DC subsets, pDC, CD16+cells
- **C:** Fibroblasts subsets, epithelial cells

B) Soluble TME

Supernatant from whole tissue culture (24h)

- **Inflammation**
- **Metabolism**
- **Angiogenesis**
- **Chemotaxis**
- **Growth factors**
- **Metalloproteases**

55 analytes quantified by Luminex, MSD and colorimetric assays

Data management and analysis

Database creation and quality controls

Biological data (236 items)

Clinical data (42 items)

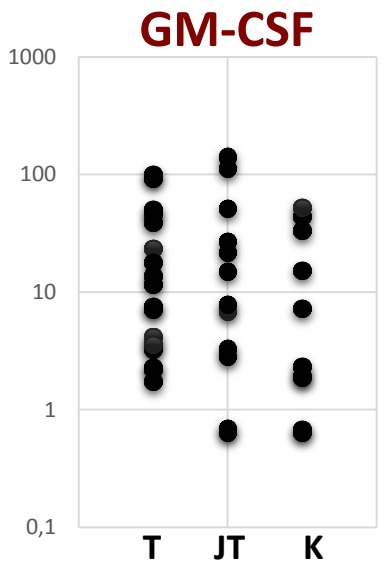
with Bioinformatics Platform and Direction des données department

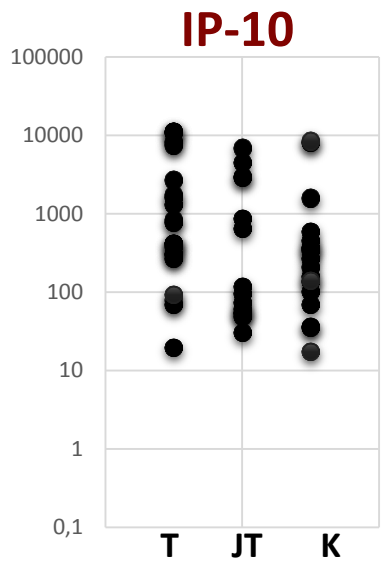
Statistical analysis

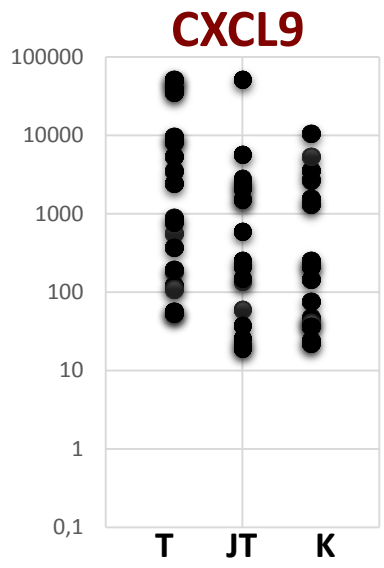
- **Descriptive analysis**
- **Association between biological parameters**
- **Association with clinical parameters**
- **Specific questions : biological knowledge driven hypothesis:**
  - **Tumor versus juxtatumors**
  - **T low versus T high**

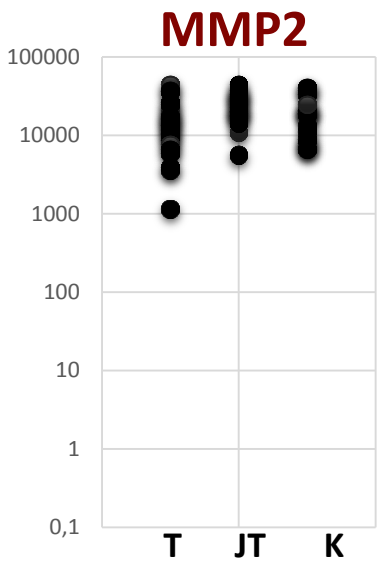
Sirven et al, manuscript in preparation

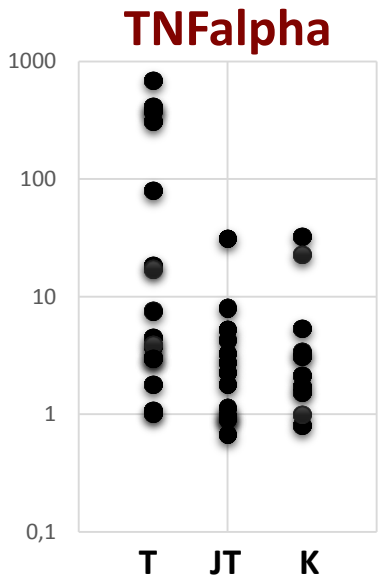
Broad profiling of tumor inflammatory mediators in ovarian cancer

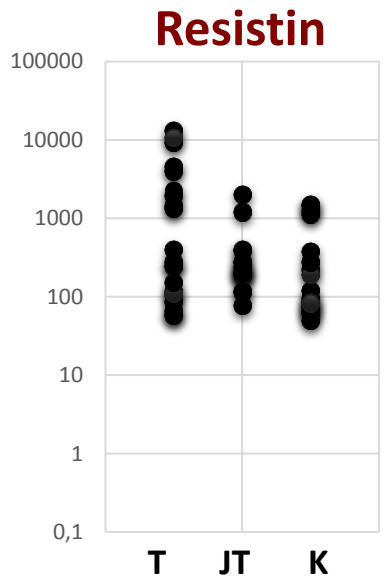


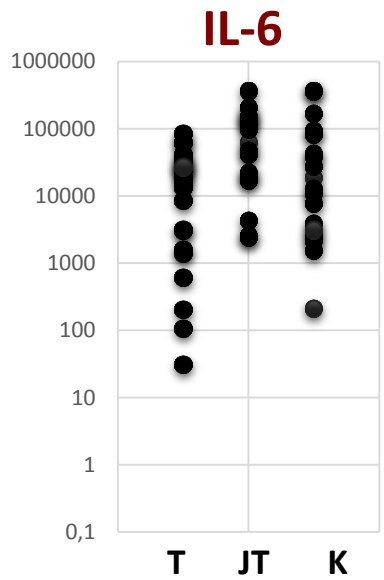


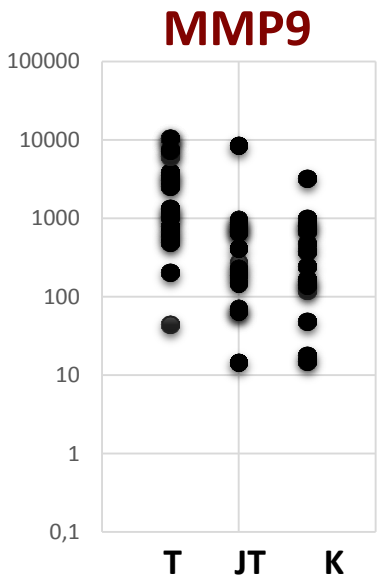












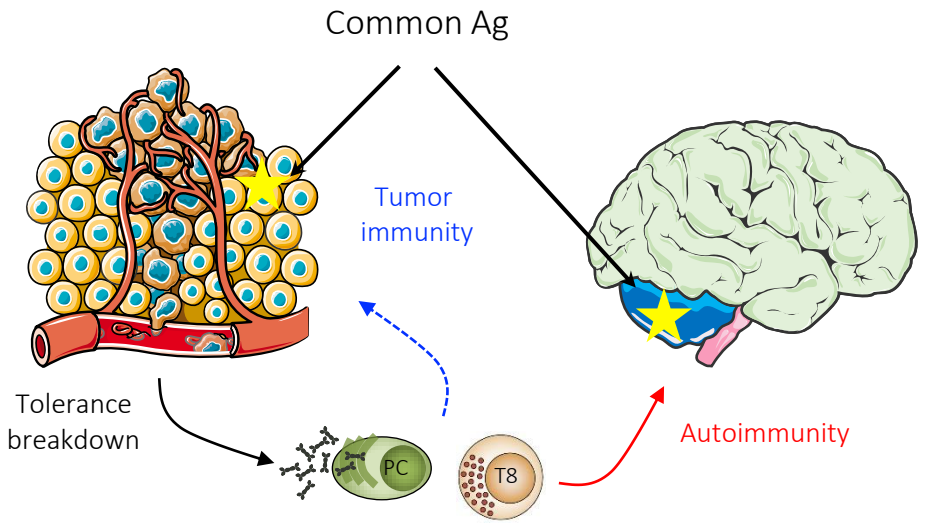
(T) Tumor n=22
(JT) Juxtatumor n=17
(K) Kystic lesion n=18

Analysis of tumors from patients with paraneoplastic neurological syndromes to study salient features and initiation of anti-tumor immunity

Institut NeuroMyoGène

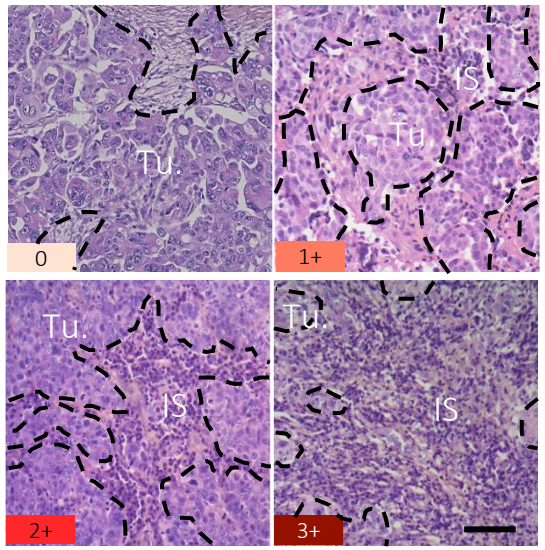
Jerôme Honnorat

Virginie Desestret



- ☞ Rare autoimmune disease
- ☞ High levels of autoAb
- ☞ Tumors often small and hard to diagnose
- ☞ Proof of efficient tumor immune surveillance?

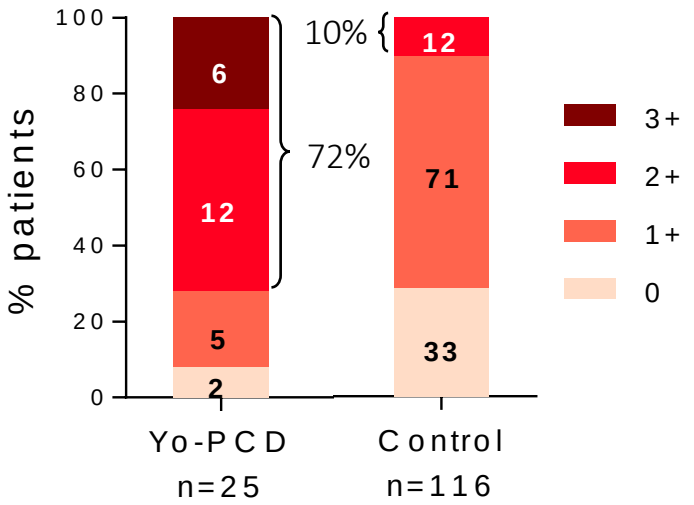
Yo paracerebellar degenerations



Quantification of the Immune infiltrate in ovarian tumors (HPS staining)

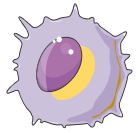
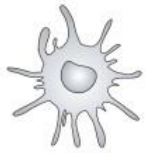
Tumor (Tu.) – Immune Stroma (IS)

Immune score



Small et al. Acta Neuropathol. 2018

Immune activating and suppressive pathways in ovarian cancer: From new mechanisms to clinical perspectives

	Anti-tumor immunity	Biomarker	Therapeutic targeting
 BDCA3^{high} DC	+	???	Activation Induction of IFN-lambda TLR-3 ligands
 Plasmacytoid DC	-	Bad prognosis	Depletion
 Inflammatory DC	???	???	???