CARE

Cancer and Autoimmune / inflammatory diseases RElationships

Coordinator: Xavier MARIETTE

Vice-coordinators: Olivier LAMBOTTE

Aurélien MARABELLE

CARE

INRA SCIENCE & IMPACT

université PARIS-SACLAY

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

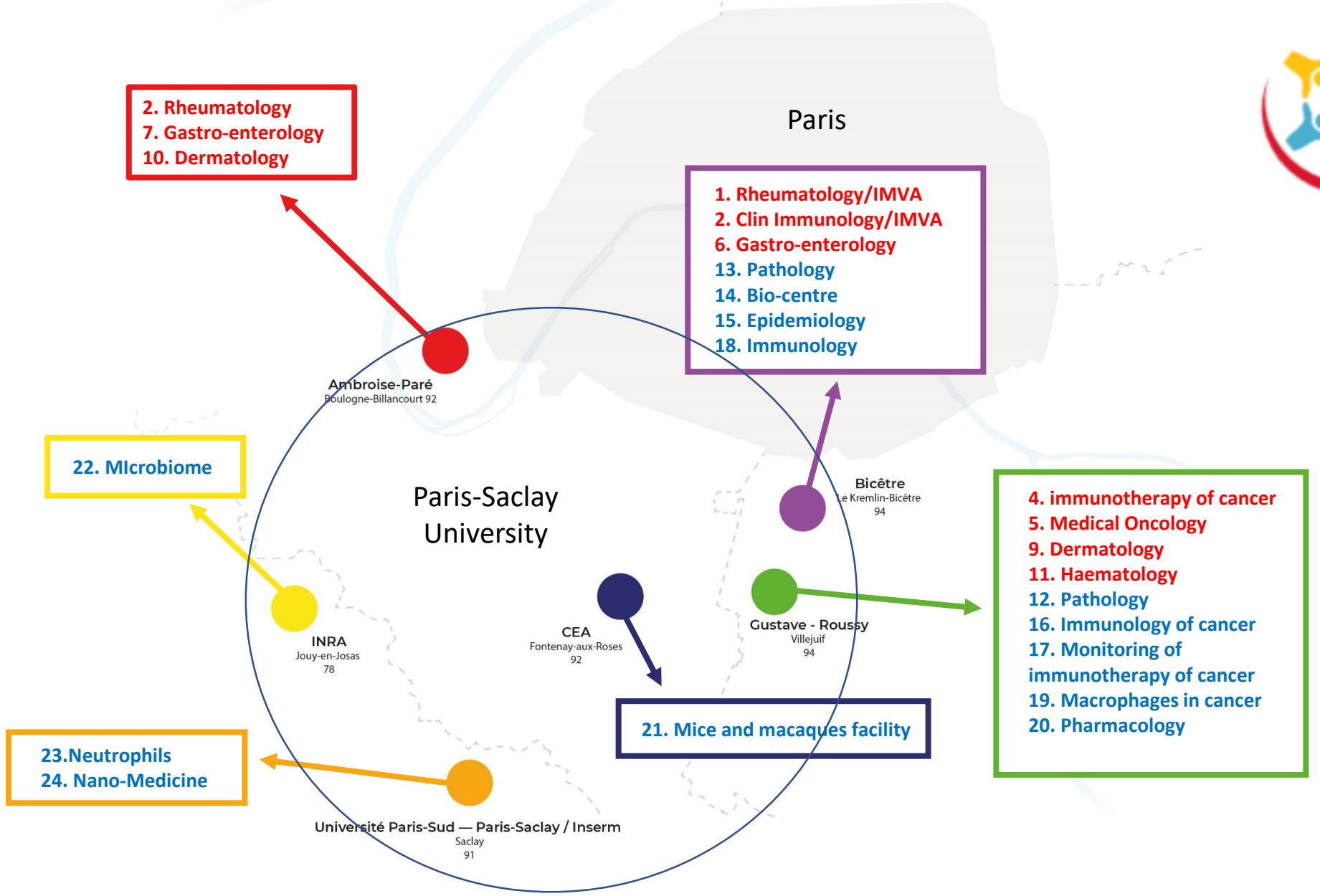
Inserm Institut national de la santé et de la recherche médicale

DE LA RECHERCHE À L'INDUSTRIE cea

Objective

- To bring together clinicians and basic scientists involved in autoimmunity/inflammation and cancer from Paris-Saclay University and Hospitals, around two **new paradigms** :
  - **Pathophysiology of cancer and autoimmune diseases (AID) may share common or opposite mechanisms**
  - **Treatment of AID and treatment of cancer are inter-related**

AP-HP.Université Paris-Saclay Hospitals and Paris-Saclay University



• The organisation of CARE: 4 work packages (WPs)

CARE

Relations between pathophysiology of AID and cancer

- **WP1: Common and opposite mechanisms involved in AID and cancer**

Relations between epidemiology and treatments of AID and cancer

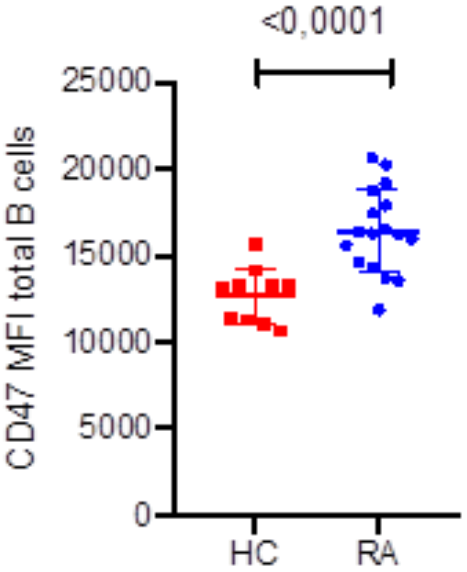
- **WP2: Autoimmunity is a risk factor of cancer**
- **WP3: Immune related adverse events (irAEs) of immunotherapy of cancer (Immune check point Blockers: ICB)**

Teaching relations between AID and cancer

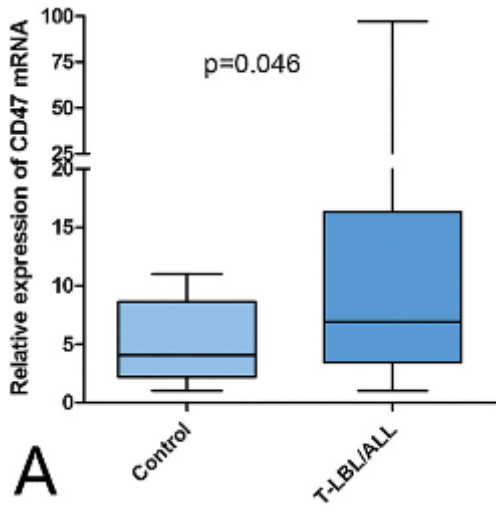
- **WP4: Teaching the new concept of cancer and autoimmunity relationships**

WP1: Common and opposite mechanisms involved in AID/ID and cancer

- Task 1: Adaptive immunity in AID and cancer
  - B cells in rheumatoid arthritis (RA) and in Sjögren's share similarities with lymphoma B cells:
    - Overexpression of CD47 ("do not eat me" receptor) in RA and in B-cell lymphoma

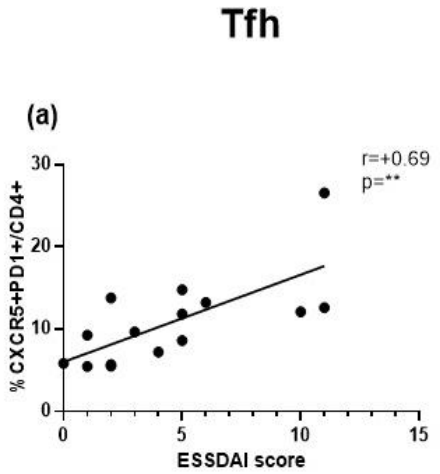


Increase in CD47 in patients with RA
X Mariette, unpublished data.

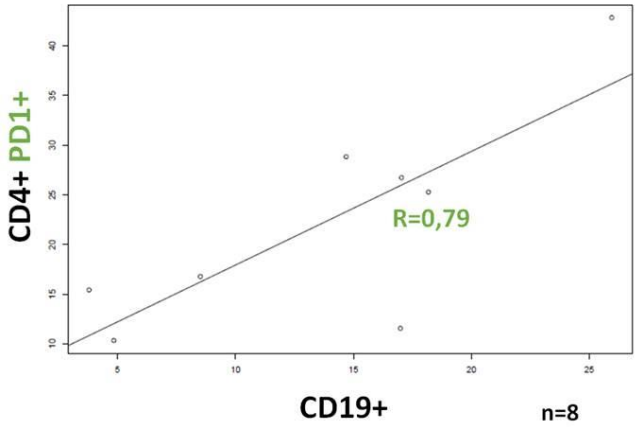


Increase in CD47 in patients with lymphoma
Yang K. Pathol Res Pract. 2019 Feb;215(2):265-271.

- The involvement of T follicular helper cells in AID and cancer
  - TFH activate plasmablasts in AID
  - TFH/cell cross talk boosts anticancer immunosurveillance



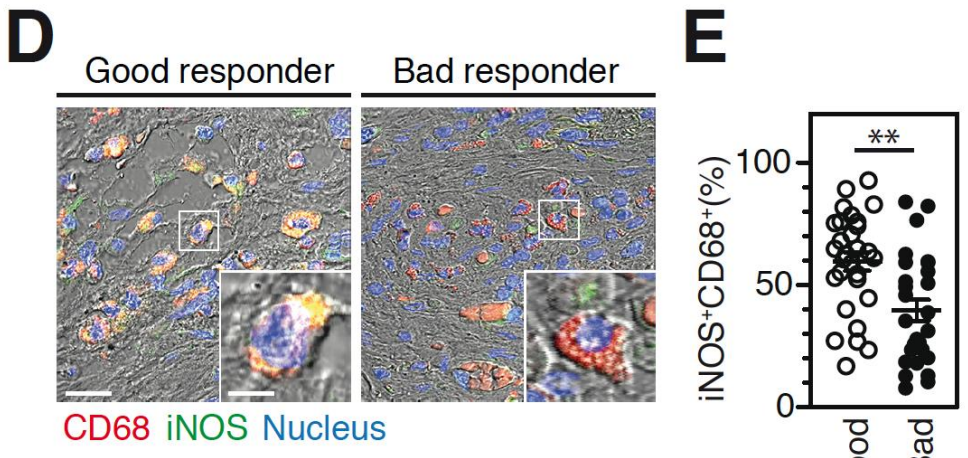
TFH correlate with activity in Sjögren's
X Mariette, unpublished data.



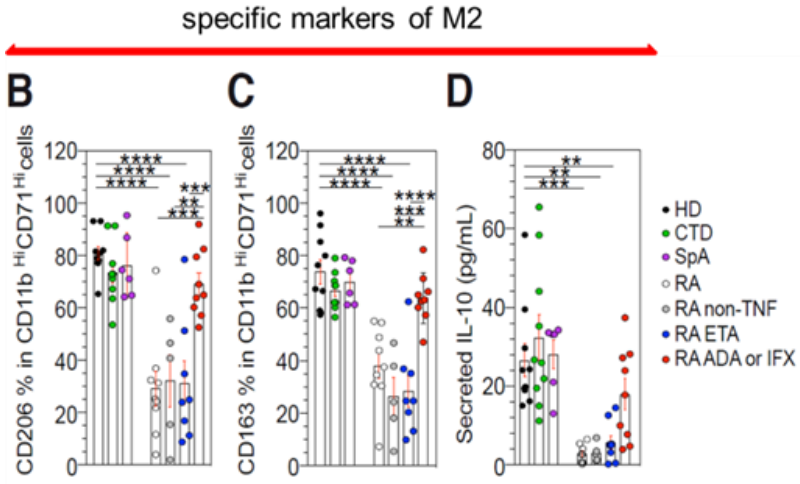
Intra-tumoral TFH correlate with B cells
A Marabelle, unpublished data.

WP1: Common and opposite mechanisms involved in AID and cancer

- <u>Task 2: Innate immunity in AID and cancer</u>
  - The balance between pro-inflammatory and anti-inflammatory macrophages in cancer and in AID
  - Dendritic cells and other myeloid cells in AID and cancer
  - Neutrophils, NETs in AID and cancer



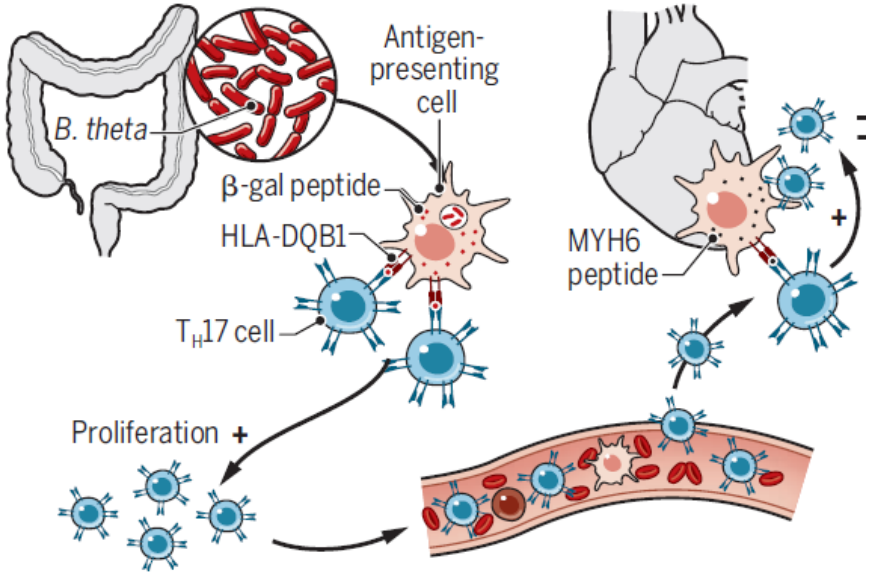
Pro-inflammatory M1 macrophages associated with cancer response
Wu, et al. CDD. 2017;24(9):1632-1644.



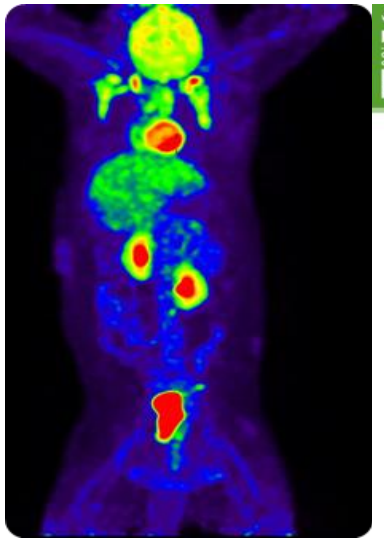
Defect of anti-inflammatory macrophages in RA
A Paoletti et al. J Immunol 2019

WP1: Common and opposite mechanisms involved in AID/ID and cancer

- Task 3: Microbiome in AID and cancer
  - Cross-reactivity between self and bacterial antigens (Gil Cruz C, Science 15 Nov 2019)
  - Cross-reactivity between tumor and bacteriophage antigens (Fluckiger et al…Zitvogel. Science in minor revision)
  - PREMIS: prospective study using meta-omics analyses of stools and immune responses to identify predictive markers of:
    - irAEs during cancer therapy with ICB
    - objective responses or hyperprogression



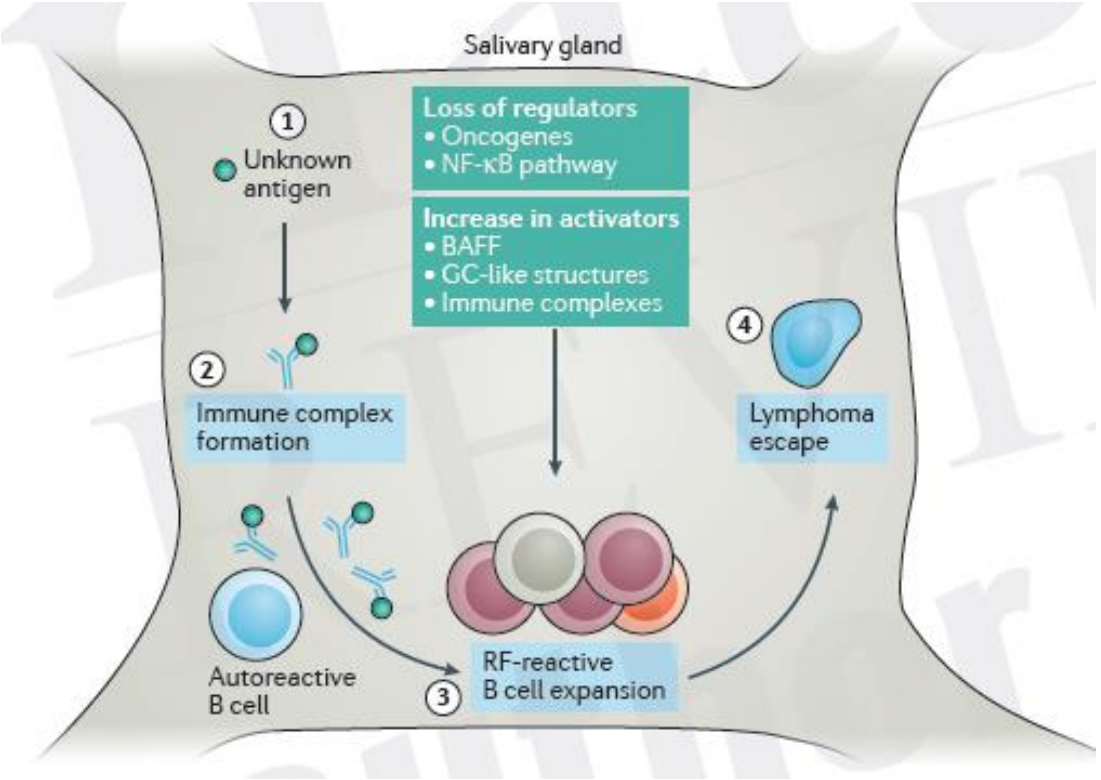
- Task 4: New technologies for in vivo imaging in animal models of AID and cancer.
  - A unique mouse and macaque facility, with mass spectrometry and advanced technics for animals imaging.
  - A new platform for **human** immune monitoring at Bicêtre in a new research building opening in 2021.



WP2: Auto-immunity is a risk factor of cancer

- Task 1: Risk of cancer in AID
  - Digestive cancers in Crohn's
  - Cutaneous cancers and psoriasis
  - Lymphoma and continuous activation of autoimmune B cells (Epidemiological and translational)
  - Role of genetic variants decreasing immune surveillance (TNFAIP3, …)

- Task 2: Incidence and evolution of AID associated with thymic malignancies
  - B Besse: National coordinator of the RYTHMIC registry



Nocturne G and Mariette X, Nat Reviews Rheumatol, 2018

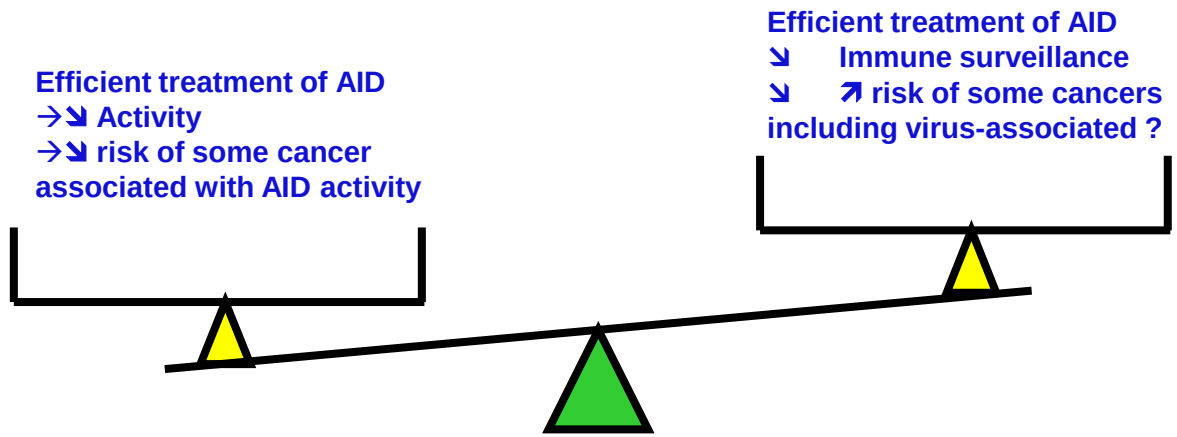
WP2: Auto-immunity is a risk factor of cancer

- Task 3: immunosuppressive drugs in AID and risk of cancer: new insights in cancer immune surveillance
  - The risk of cancer with TNF inhibitors (TNFi) in inflammatory bowel diseases
  - The risk of cancer with TNFi and other biologics in rheumatic diseases.
    - Use of the French SNDS (R Seror)
  - The effect of TNFi on immunosurveillance

Table 3. HRs Comparing the Risk of Lymphoma in Patients Exposed to Thiopurine Monotherapy, Anti-TNF Monotherapy, and Combination Therapy vs Unexposed Patients

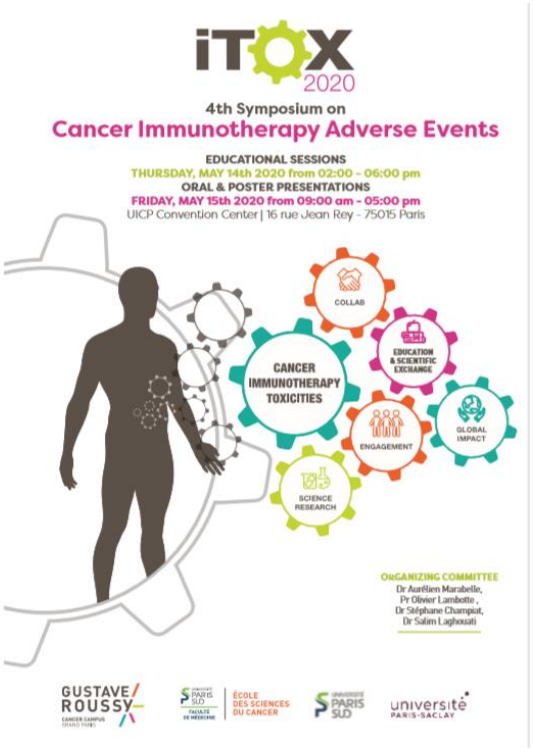
	Exposed to Thiopurine Monotherapy vs Unexposed to Thiopurines or Anti-TNF Agents		Exposed to Anti-TNF Monotherapy vs Unexposed to Thiopurines or Anti-TNF Agents		Exposed to Combination Therapy vs Unexposed to Thiopurines or Anti-TNF Agents	
Lymphoma Type	Crude HR (95% CI)	Adjusted HR (95% CI)[a]	Crude HR (95% CI)	Adjusted HR (95% CI)[a]	Crude HR (95% CI)	Adjusted HR (95% CI)[a]
All Patients						
All lymphoma	2.06 (1.58-2.70)	2.60 (1.96-3.44)	1.57 (1.08-2.28)	2.41 (1.60-3.64)	3.60 (2.10-6.19)	6.11 (3.46-10.8)
Hodgkin lymphoma	2.78 (1.45-5.33)	2.83 (1.37-5.84)	2.21 (0.92-5.35)	2.23 (0.81-6.13)	11.4 (4.76-27.2)	12.1 (4.46-33.1)
Non-Hodgkin lymphoma	1.95 (1.45-2.62)	2.57 (1.90-3.49)	1.47 (0.97-2.22)	2.48 (1.58-3.89)	2.38 (1.17-4.84)	4.48 (2.15-9.34)
Patients With Incident IBD						
All lymphoma	1.58 (0.84-3.00)	2.35 (1.16-4.75)	0.98 (0.39-2.48)	1.49 (0.54-4.12)	3.14 (1.13-8.71)	5.90 (1.79-19.4)

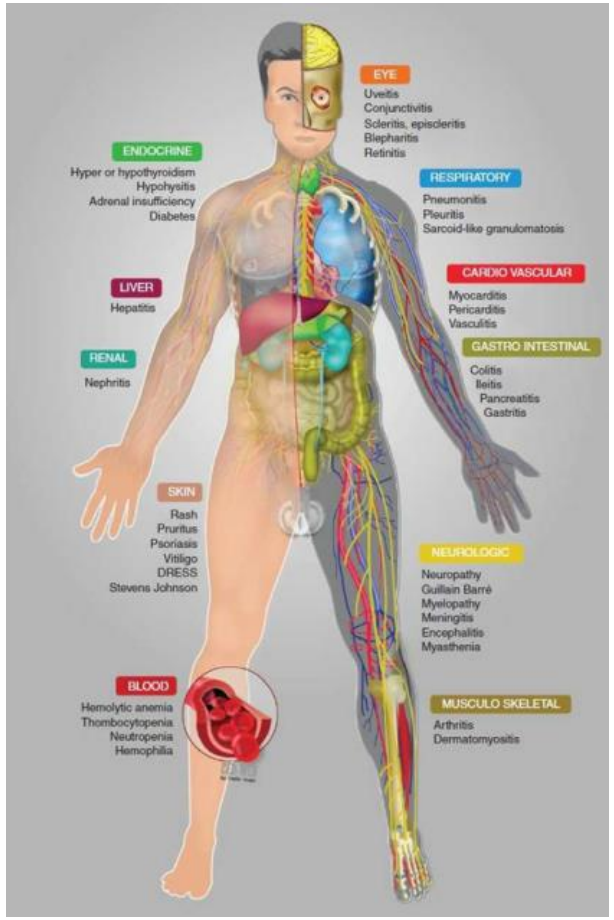
Lemaitre, et al. *JAMA*. 2017;318(17):1679-1686.



WP3: Immune related adverse events of immunotherapy of cancer

- Task 1: Immunotox: a clinical network for managing immune IrAEs of Immune Checkpoint Blockers
  - Organized by O Lambotte and A Marabelle
  - Associated with a national board and educational program





WP3: Immune related adverse events of immunotherapy of cancer

- Task 2: Inducing or modulating autoimmunity for curing cancer

IrAEs are associated with better cancer control

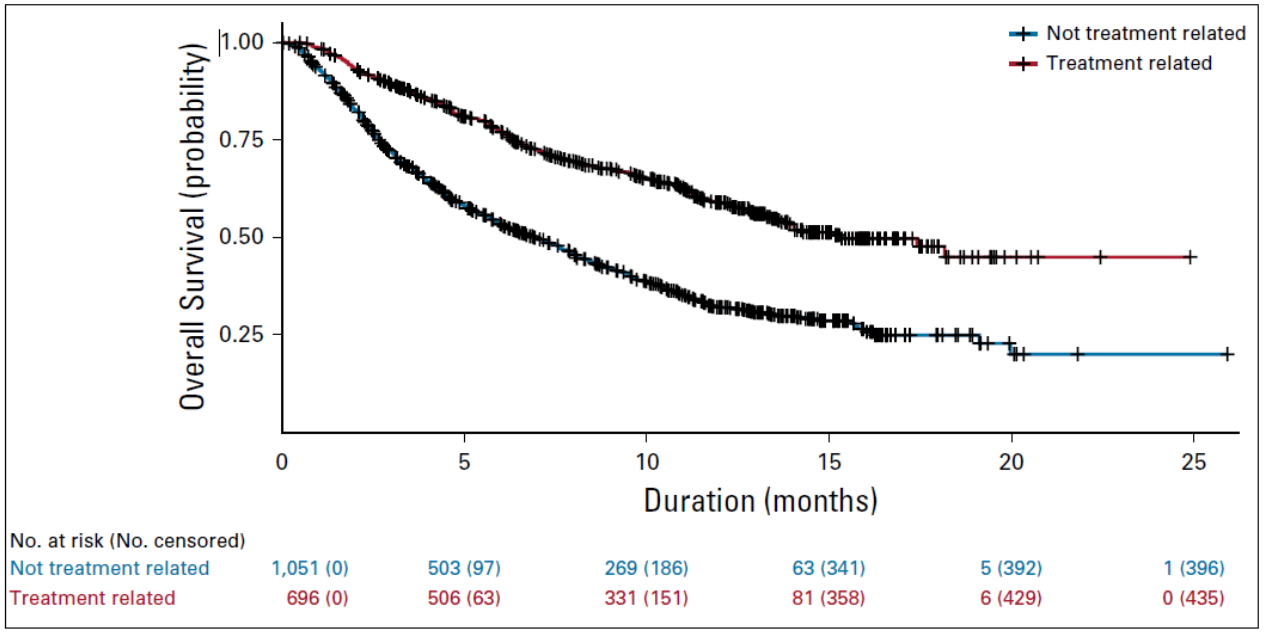
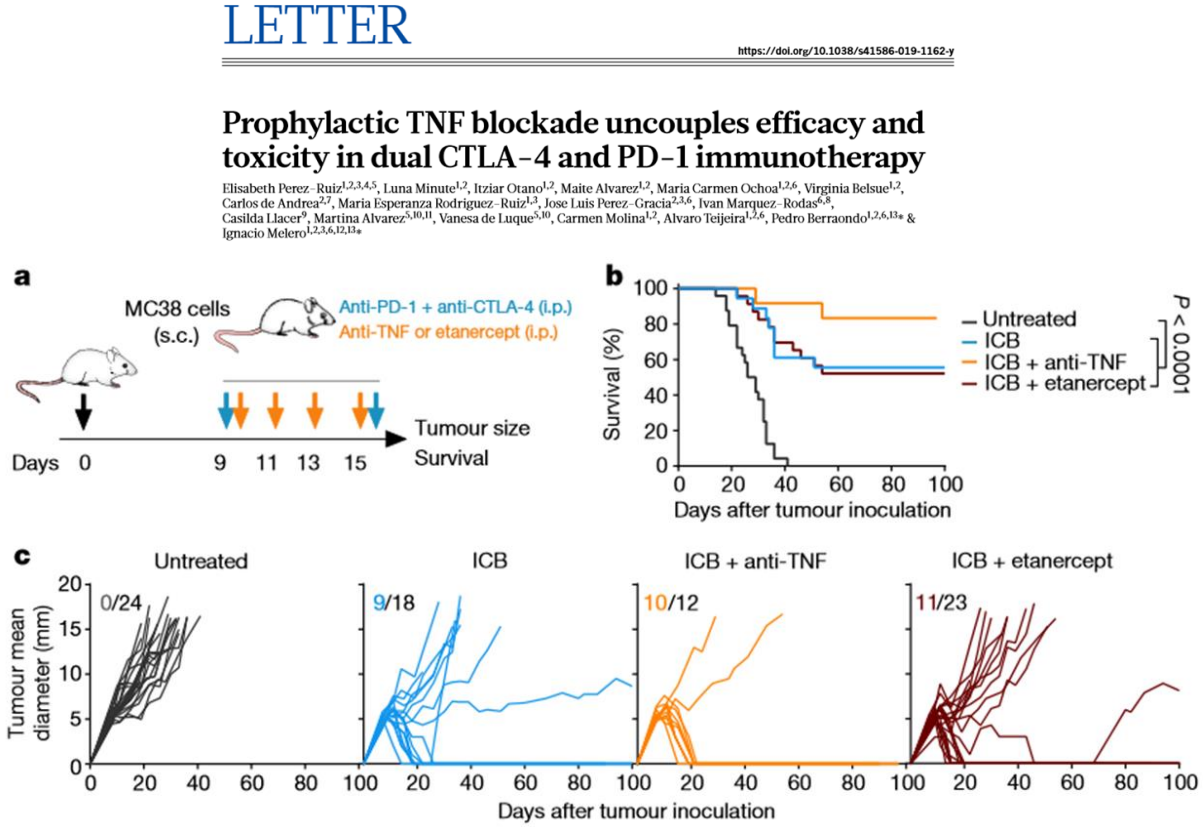


FIG 1. Overall survival, adjusted for trial, age, sex, performance status, and liver metastases (yes/no), in patients who did and did not report treatment-related adverse events of special interest. Includes data from all seven trials.

Maher VE et al. J Clin Oncol. 2019 May 22

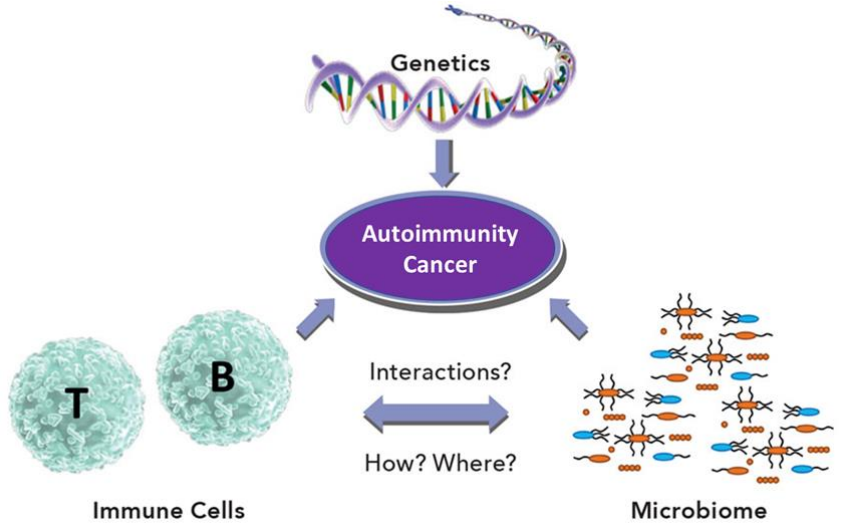
In mice models, association of anti-TNF to ICB increase survival of mice



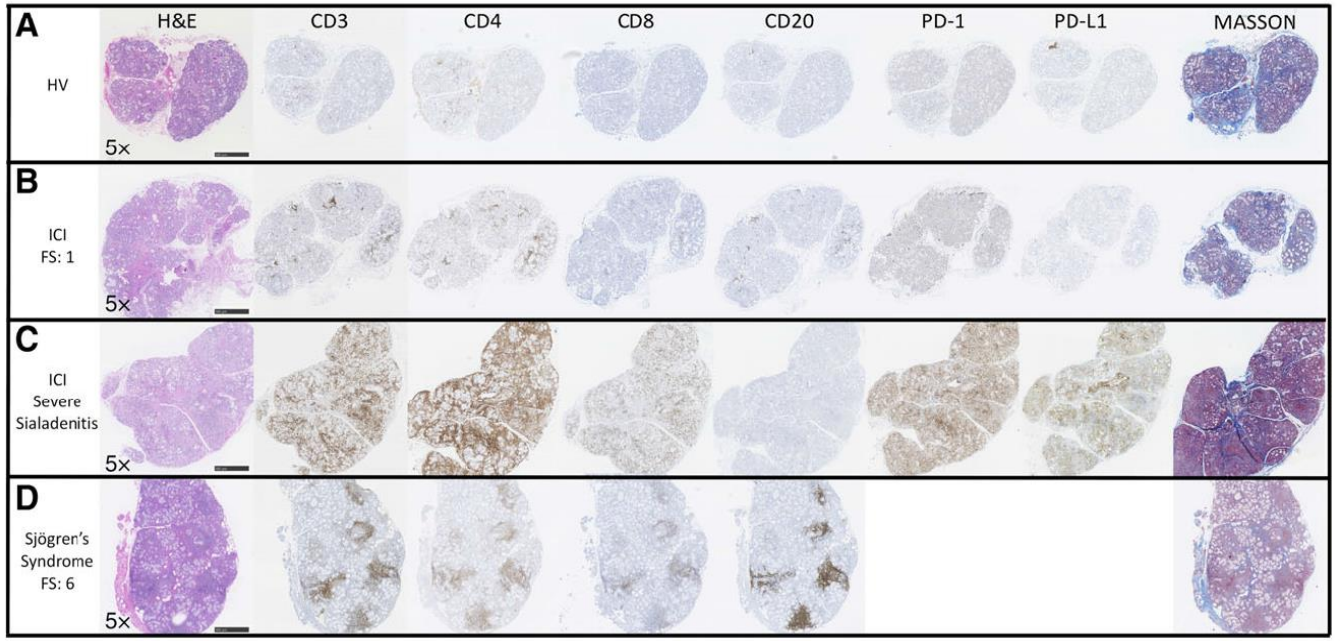
Perez-Ruiz E et al. Nature. 2019 May;569(7756):428-432

WP3: Immune related adverse events of immunotherapy of cancer

- Task 3: Modulating microbiome for treating AID and cancer
  - IGR/ Bicêtre will launch pilot studies of faecal microbial transplantation in NSCLC/RCC/melanoma



- Task 4: IrAEs may give a new vision of pathophysiology of AID
  - A unique opportunity to capture the beginning of autoimmunity
  - IrAEs are different from “classical” AID



Sicca syndrome after ICI is different from Sjögren’s syndrome
Warner BM. The Oncologist. 2019

WP4: Teaching the new concept of cancer and autoimmunity relationships

MEDICAL STUDENTS

Specific course on AID/Cancer relationships in the Immunology course early in the 2nd year of the medical studies

MASTERS AND PhD STUDENTS

Dedicated module on AID/Cancer relationships in the Masters of Paris Saclay University:

- Immunology
- Cancerology
- Therapeutic innovation

ENGINEERING STUDENTS

Specific module for students engineers in the Institut de Formation Supérieure Biomédicale (IFSBM)

NURSES

Specific course in the new Master for Nurses in Advanced Practices (master IPA) at Paris Saclay University, dedicated to nurses and health professionals

The governing boards of CARE

Management committee

16 Members

- The coordinator and the 2 co-coordinators
- The 4 WP leaders
- 2 clinicians representing AID and cancer
- 3 researchers representing AID, cancer and microbiome
- 6 representatives
  - **AP-HP**
  - **INSERM**
  - **Paris-Saclay University**
  - **IGR**
  - **CEA**
  - **INRA**

Executive committee

9 Members

- The coordinator and the 2 co-coordinators
- 4 Tasks leaders
- The project manager
  - provided by AP-HP
- The “Chef de Clinique”
  - provided by the University

External Scientific advisory board

8 Members

- Pr Antony Rosen
  - J Hopkins, Baltimore,
- Pr Len Calabrese
  - Cleveland clinic
- Pr François Ghiringhelli
  - Dijon University
- 2 Representatives of the patient’s associations for AID and cancer,
- 3 Representatives of the pharmaceutical industries supporting the project

Conclusion

- **CARE will have a structural effect**
  - Bringing together teams from **Paris-Saclay Hospitals**, **Gustave Roussy Institute** and **Paris-Saclay University's labs** involved in autoimmunity/inflammation and cancer

- **CARE is based on 2 new paradigms**
  - Pathophysiology of **AID and cancer share common or opposite mechanisms**
  - Treatment of AID and cancer are interrelated

- **CARE will boost university and hospital relationships and will improve:**
  - **Care:** the Immunotox network and better management of immunosuppressive drugs in AID.
  - **Teaching:** new courses to specialists of different fields (MD, PhD, Engineers, nurses).
  - **Research**: translational, clinical and epidemiological research thanks to the different expertise