LE « SOI ÉTENDU » : LE POINT DE VUE DU PHILOSOPHE

Académie nationale de Pharmacie, Paris, France
6 février 2019

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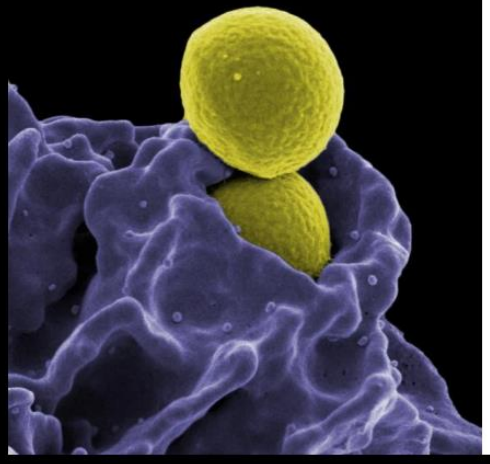
QUESTION: IS THERE ROOM FOR A DIALOGUE BETWEEN IMMUNOLOGY AND PHILOSOPHY?



- Individuality
- What triggers an immune response

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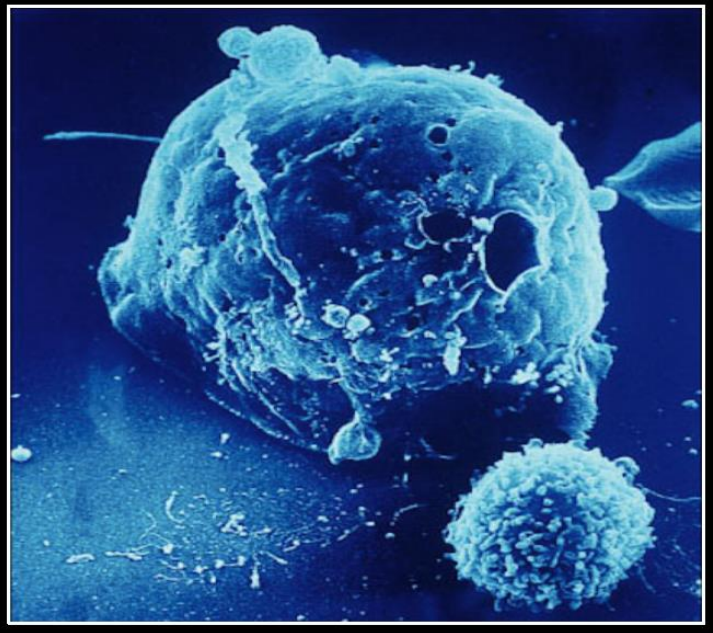
ERC PROJECT "IDEM": "IMMUNITY, DEVELOPMENT AND THE MICROBIOTA: UNDERSTANDING THE CONTINUOUS CONSTRUCTION OF BIOLOGICAL IDENTITY"

- **2015-2020**
- Microbiota, physiological individuality, and "holobiont"
- Role of the **microbiota,** at the interface between developmental biology, microbiology, immunology, the neurosciences, medical fields (rheumatology, gastroenterology, etc.).
- => **Philosophy** and/as **interdisciplinarity**.

PLAN



1. Immunology and individuality: Self-nonself
2. Immunology and individuality: the organism as an ecosystem in the context of research on the microbiota ("extended self")
3. Three examples of therapeutic consequences

1. IMMUNOLOGY AND INDIVIDUALITY: SELF-NONSELF

THE STORY OF THE DIALOGUE BETWEEN IMMUNOLOGY AND PHILOSOPHY

Individuality
- Unity
- Boundaries
- Uniqueness

Self/
Nonself

Burnet (1899-1985)

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IMMUNOLOGY AND INDIVIDUALITY: A LONG HISTORY

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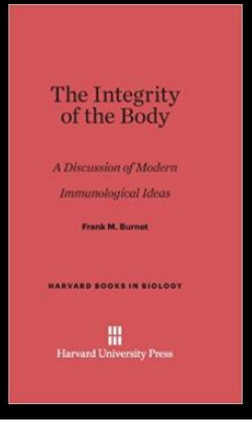
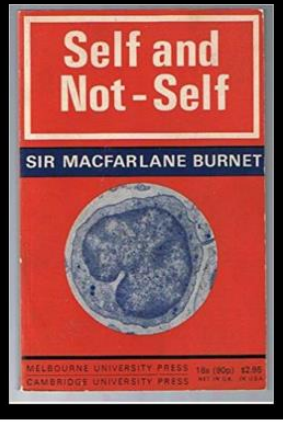
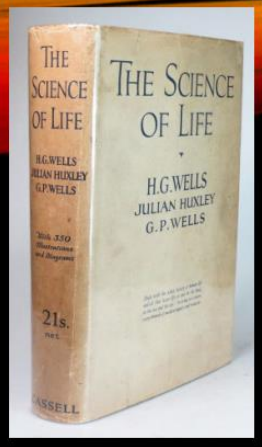
- **"Individuality" in immunology** (Richet 1894, 1913; Loeb 1930, 1937; Medawar 1957; Burnet 1962; Hamburger 1978).
- **Self-nonself ('notself')** (Burnet 1937, 1949, 1962, 1969).
  - ✓Acceptance of self
  - ✓Rejection of nonself





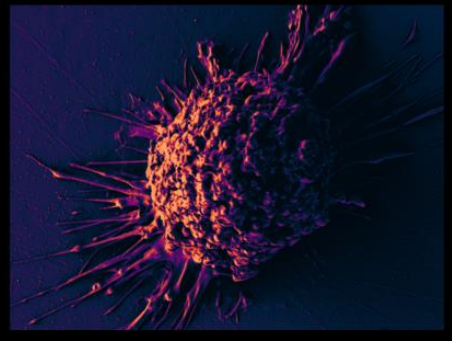


BURNET IS INSPIRED BY PHILOSOPHY WHEN HE USES THE WORD 'SELF'

- *The Science of Life* (1929)
- Psychology.
- Self (Locke, *Essay on Human Understanding*, 2nd ed., 1693)
- Burnet often insisted that self/not-self was (also) a philosophical question.

PROBLEMS WITH SELF-NONSELF

- **Immune response to cancerous tumors.** Tautology of the "altered self".
- **Autoreactivity and autoimmunity.**
- **Immune tolerance.**



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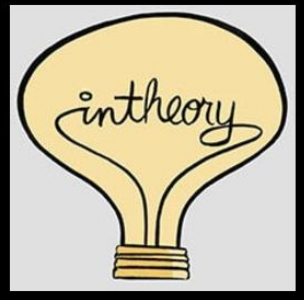
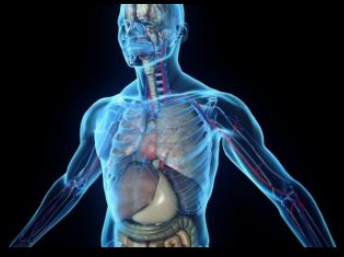
A DOUBLE ALTERNATIVE TO SNS





- SNS is both a **theory** and a **conceptual framework** to account for **biological individuality**.
- Necessity to build:
  - Another conceptual framework to account for biological individuality
  - Another immunological theory

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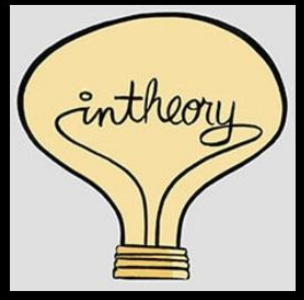
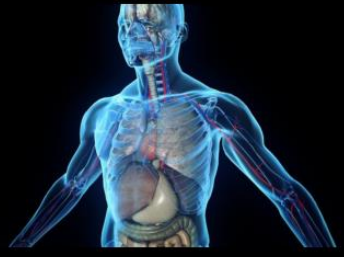
A DOUBLE ALTERNATIVE TO SNS





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2. IMMUNOLOGY AND INDIVIDUALITY: THE ORGANISM AS AN ECOSYSTEM IN THE CONTEXT OF RESEARCH ON THE MICROBIOTA ("EXTENDED SELF")

EVERY ORGANISM IS A COMPLEX "MICROBIAL" ECOSYSTEM

- A **complex ecosystem** made of many biotic elements, belonging to different species, and even kingdoms.
- Huge numbers of **resident microbes**.
- Microbiota: **bacteria**, but also **viruses** and **fungi**.
- In the gut, but also **all body's interfaces**.
- Some of these microbes play a **functional**, sometimes indispensable, role.
- They are ***not* rejected by the immune system**.

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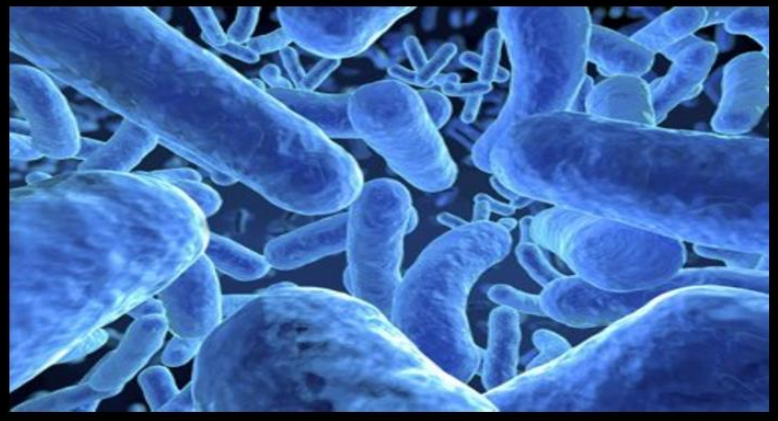
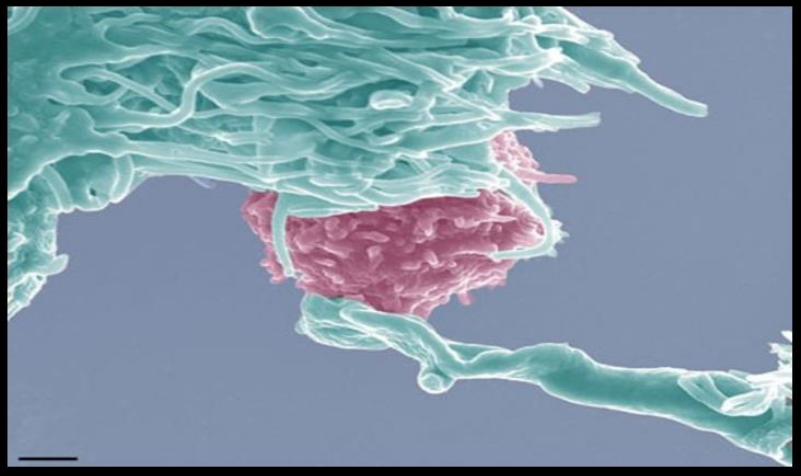
PHYSIOLOGICAL ROLES OF THE MICROBIOTA



- What it does.
- **Digestion, metabolism, immunity, development.**
- Brain function and behavior. (Cryan & Dinan 2012).
- Often: **mutualism** (though it can change).
- Components of the microbiota are **not necessarily beneficial!** (Pathobionts, etc.)
- The constant construction of an **equilibrium.**

THE CONTINUOUS UNIFICATION OF A PLURALITY OF CONSTITUENTS



- Every organism is an ecosystem, but a **strongly unified ecosystem**.
- Role of **immune system in this unification of a plurality**:
  - Inclusion/exclusion. Not endogenicity.
  - Cohesiveness (including communication)
- Via **different activities:** not only defense, but also development, repair, and other forms of regulation.
- ***E pluribus unum***
  - Pradeu, What is an organism? An immunological answer (2010).
- True **across species.**

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"CO-IMMUNITY"

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Lynn Chiu

Thierry Schaeverbeke

Laurence Delhaes

Marie-Elise Truchetet

Thomas Bazin

C·H·U Hôpitaux de Bordeaux

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université de BORDEAUX

frontiers in Immunology

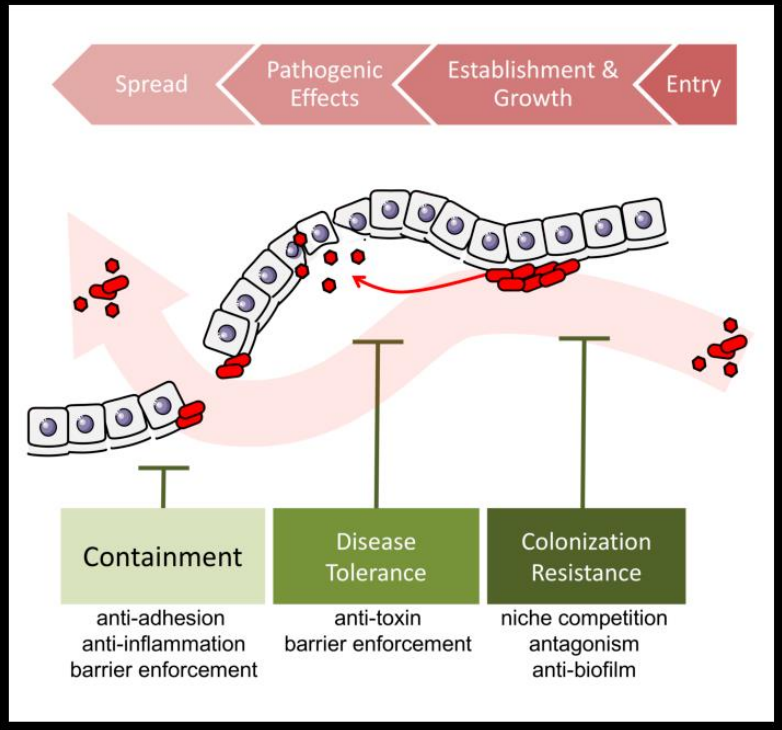
December 2017 | Volume 8 | Article 1678

Protective Microbiota: From Localized to Long-Reaching Co-Immunity

Lynn Chiu[1†], Thomas Bazin[2,3†], Marie-Elise Truchetet[4], Thierry Schaeverbeke[2,4], Laurence Delhaes[5,6] and Thomas Pradeu[1]*

Thomas Bazin

DIFFERENT STAGES, DIFFERENT MICROBIAL INTERVENTIONS



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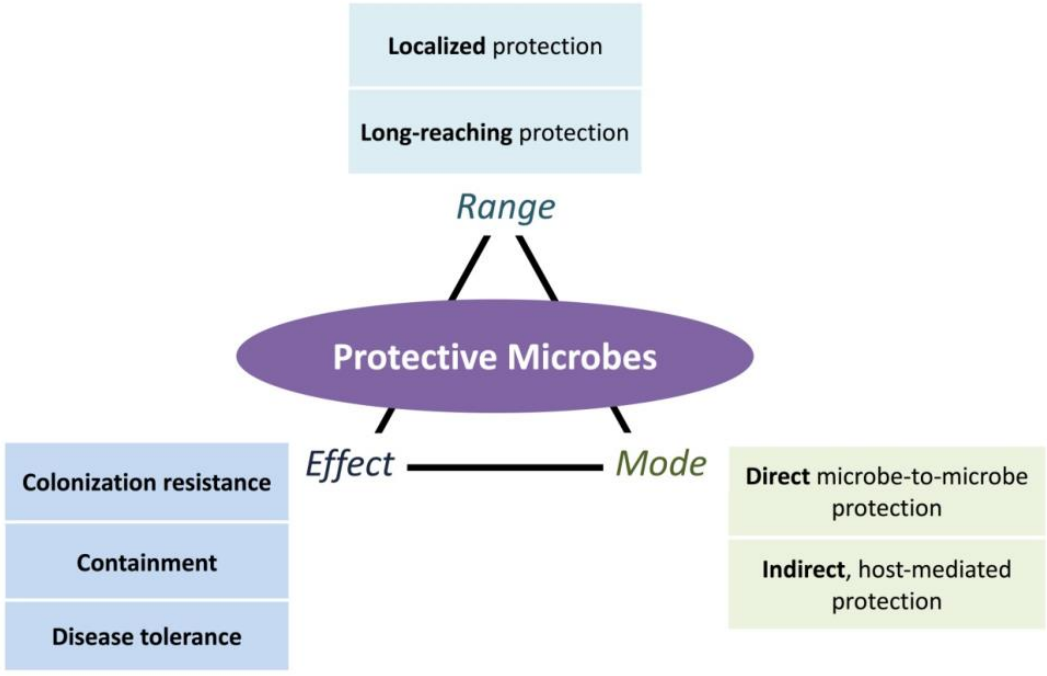

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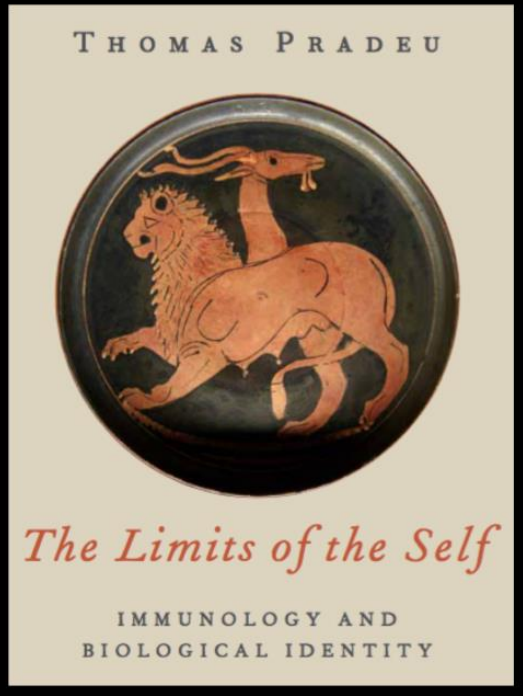
EVERY ORGANISM IS AN IMMUNOLOGICALLY UNIFIED CHIMERA



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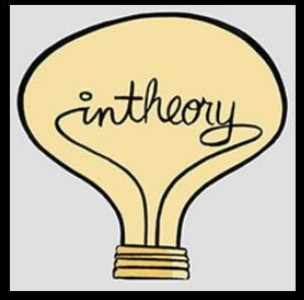
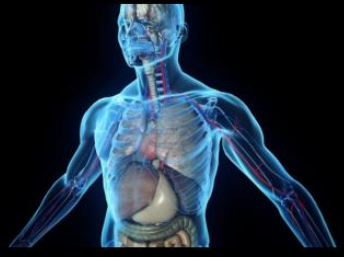
Oxford Univ. Press, paperback (2019)

A DOUBLE ALTERNATIVE TO SNS





- SNS is both a theory and a conceptual framework to account for biological individuality.
- Necessity to build:
  - Another conceptual framework to account for biological individuality
  - **Another immunological theory -> Discontinuity theory of immunity**

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FROM THE CRITIQUE OF THE SELF-NONSELF THEORY TO THE CONSTRUCTION OF THE DISCONTINUITY THEORY

On the definition of a criterion of immunogenicity

Thomas Pradeu*† and Edgardo D. Carosella‡

PNAS | November 21, 2006

PERSPECTIVES

ESSAY

The speed of change: towards a discontinuity theory of immunity?

Thomas Pradeu, Sébastien Jaeger & Eric Vivier

NATURE REVIEWS | IMMUNOLOGY
OCTOBER 2013

IMMUNOLOGY

The discontinuity theory of immunity

Thomas Pradeu[1]* and Eric Vivier[2,3]*

SCIENCE IMMUNOLOGY | PERSPECTIVE

14 July 2016

2018

Trends in Immunology

Forum

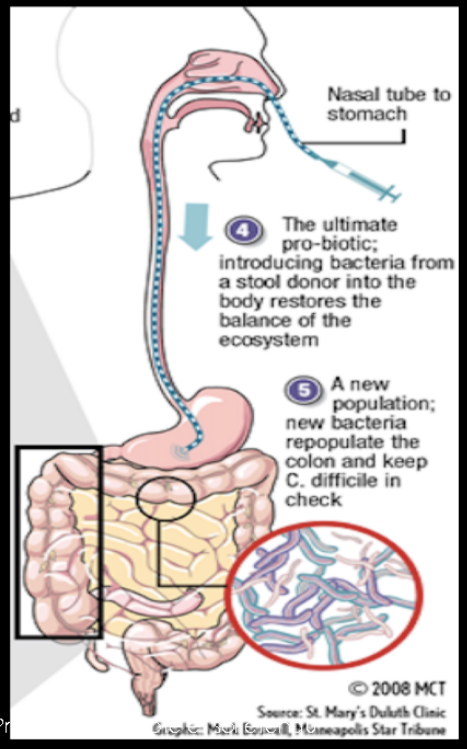
Towards a General Theory of Immunity?

Gérard Eberl[1,2,*] and Thomas Pradeu[3,*]

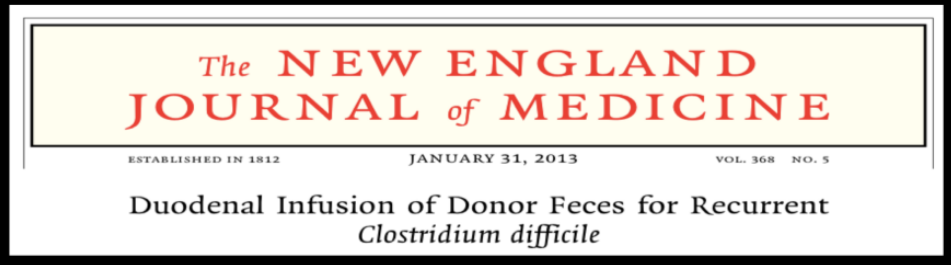
CellPress REVIEWS

3. THREE EXAMPLES OF THERAPEUTIC CONSEQUENCES

CONSEQUENCE 1: FMT : TOWARDS AN "ECOSYSTEMIC" MEDICINE?



- Not necessarily **fighting** microbes
- **Restoring body's equilibria**
- **Maintaining/stimulating symbionts** (e.g., Barton et al., Herpesvirus latency confers symbiotic protection from bacterial infection, *Nature*, 2007). One of our best immune defenses!
- Injection of **symbiont products**, e.g., PSA.
- **Establishing a new gut ecosystem**. A case for fecal transplantation.


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 31, 2013 VOL. 368 NO. 5

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

CONSEQUENCE 2: CANCER THERAPIES

- Microbiome can influence patients' responses to:
  - Chemotherapy
  - Immunotherapy

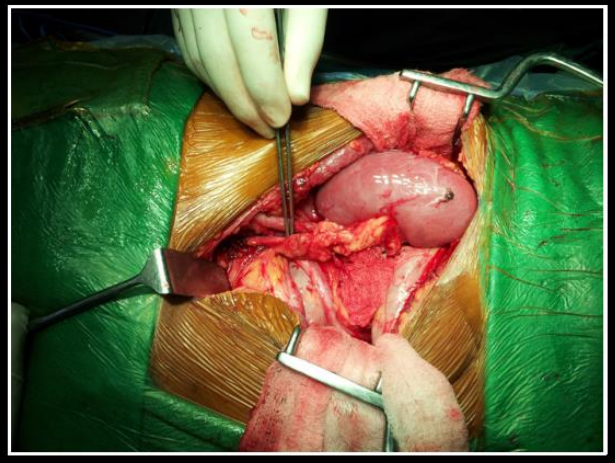
- Routy et al. (2018), Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors.
- Gopalakrishnan et al. (2018), Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients.
- Matson et al. (2018), The commensal microbiome is associated with anti–PD-1 efficacy in metastatic melanoma patients.

REVIEW

The microbiome in cancer immunotherapy: Diagnostic tools and therapeutic strategies

Laurence Zitvogel,[1,2,3,4*] Yuting Ma,[5,6] Didier Raoult,[7] Guido Kroemer,[8,9,10] Thomas F. Gajewski[11*]

CONSEQUENCE 3: A ROLE FOR THE MICROBIOTA IN TRANSPLANTATION

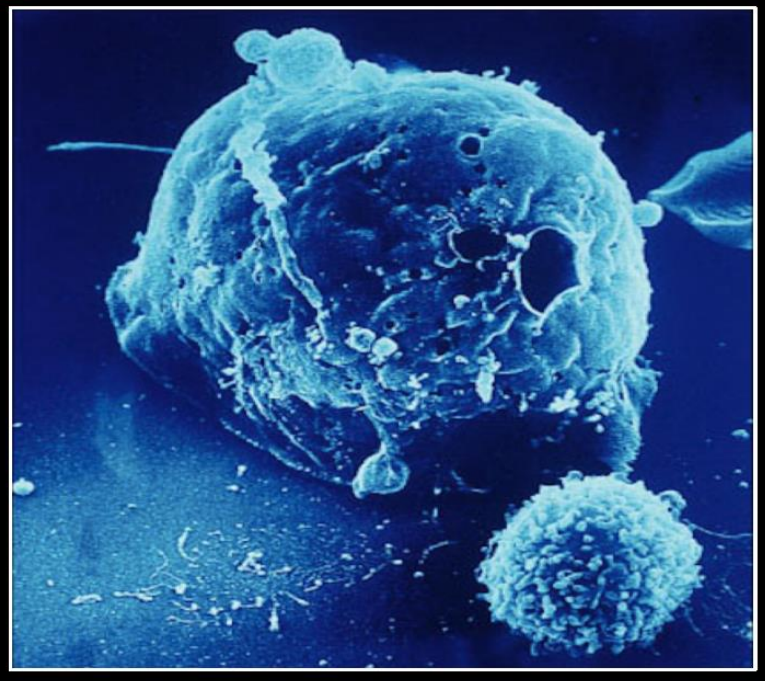


- A major challenge in transplantation studies is to determine whether the **microbiota may influence rejection responses**, and how the **microbiota is modified by** (and perhaps modifies itself) the effect of **immunosuppressive drugs** after a transplantation.

Immunosuppressive Treatment Alters Secretion of Ileal Antimicrobial Peptides and Gut Microbiota, and Favors Subsequent Colonization by Uropathogenic *Escherichia coli*

Jérôme Tourret, MD, PhD,[1,2,3] Benjamin P. Willing, PhD,[1,4] Sara Dion, RLAT,[3,5] Jayden MacPherson, BSc,[4] Erick Denamur, MD, PhD,[3,5] and Brett B. Finlay, PhD[1]

***Transplantation* (2017)**

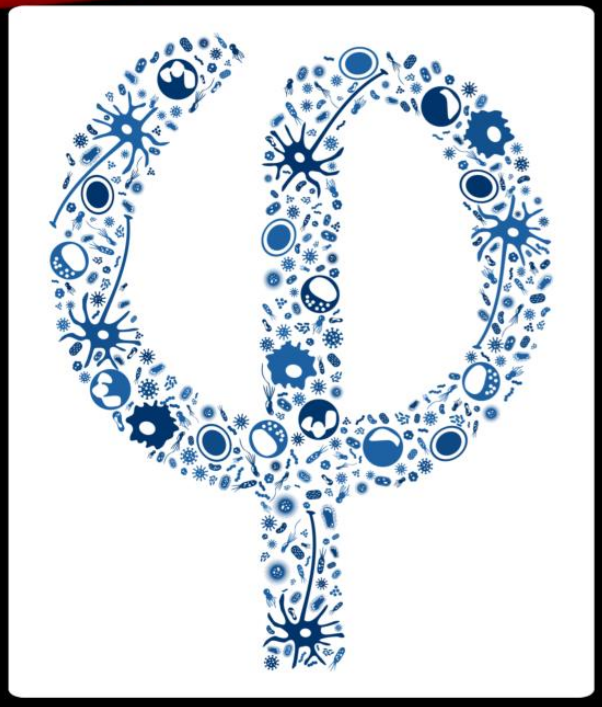


TO SUM UP

- Two main points:

1. A novel approach to biological individuality: immunologically unified chimeras
2. A novel theoretical approach for immunology

- Such re-conceptualizations can have experimental and clinical consequences
- Urgent need for stronger collaborations between scientists and philosophers, in immunology and beyond.



Why science needs philosophy

Lucie Laplane[a,b,1], Paolo Mantovani[c,1], Ralph Adolphs[d], Hasok Chang[e], Alberto Mantovani[f,g], Margaret McFall-Ngai[h], Carlo Rovelli[i], Elliott Sober[j], and Thomas Pradeu[k,b,2]

PNAS, March 2019

ACKNOWLEDGMENTS

- Pradeu group in Bordeaux
- ImmunoConcEpT unit (UMR5164).
- This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme - grant agreement #637647 – IDEM.