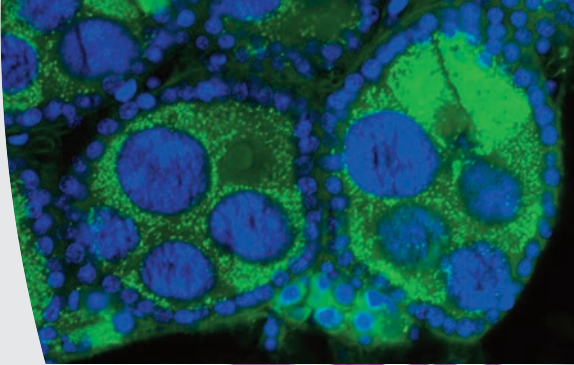
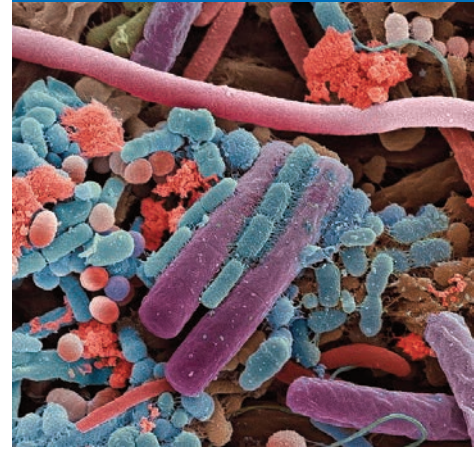




INSTITUT DE FRANCE
Académie des sciences



Symbiose et cohabitation *Symbiosis and cohabitation* Colloque en anglais

25 avril 2017 de 9h30 à 17h00
Grande salle des séances
de l'Institut de France
23, quai de Conti, 75006 Paris

Les interactions symbiotiques sont beaucoup plus répandues que ce que l'on pensait jusqu'à récemment. Ce qui était souvent considéré comme une simple cohabitation d'un organisme supérieur avec des microorganismes commensaux se trouve être une véritable association à bénéfices réciproques, avec échanges multiples de signaux entre partenaires. L'essor de la métagénomique et de la biologie cellulaire permet maintenant une analyse beaucoup plus détaillée de ces interactions. Le principal modèle de symbiose étudié au niveau moléculaire a été l'interaction entre légumineuses et la bactérie *Sinorhizobium* qui aide la plante à fixer l'azote atmosphérique. De nombreuses autres symbioses sont maintenant à l'étude.

L'objectif de ce colloque est de faire le point de nos connaissances, notamment sur ces nouveaux modèles d'interaction et d'en comprendre les mécanismes et la signalisation. Les exemples traités porteront sur les associations symbiotiques bactéries-coraux ou autres organismes marins, bactéries-insectes et aussi les symbioses bactéries-homme ou -animaux de laboratoire. Ils illustreront en particulier comment les interactions symbiotiques entre les microbiotes et les organismes qu'ils colonisent jouent un rôle dans leur biologie, le développement du système immunitaire et la réponse aux pathogènes. Les implications de ces découvertes en termes de protection de la santé humaine ou animale, de production végétale et de protection de l'environnement seront discutées par les intervenants.

Presentation

Symbiotic interactions are more common than we thought a few years ago. What was considered a simple cohabitation of organisms with commensal microorganisms is finally a true association with reciprocal benefits and with multiple signal exchanges between partners. Nowadays, the rise of metagenomics and cellular biology allows a more detailed analysis of these interactions. The interaction between leguminous plants and *Sinorhizobium*, which helps them to fix nitrogen from the atmosphere, has been the most studied model of symbiosis at the molecular level. Numerous other symbioses are currently being studied.

The aim of this colloquium is to review our knowledge in the matter, mainly on the new models of interaction and improve our understanding of signal mechanisms. Examples will focus on bacteria-algae or other sea organisms symbiotic associations, as well as bacteria-insect and also bacteria-human or -laboratory animals symbiosis. They will mainly illustrate how symbiotic interactions between microbiota and colonizing organisms play a part in their biology, immunity system development and pathogen response. Implications of these discoveries, in terms of human or animal health protection, vegetal production and environment protection will be discussed by the speakers.



Colloquium organised by



Pascale COSSART

Secrétaire perpétuel, Académie des sciences, Professor, Pasteur Institute, France

Pascale Cossart is professor at Pasteur Institute. Her research focuses on the study of molecular and cellular mechanisms implicated in bacterial infections, using the bacterium *Listeria monocytogenes* as a model. Pascale Cossart was a pioneer in a discipline that she named “Cellular Microbiology”. She highlighted numerous strategies used by bacteria during infection. Her work has led to new concepts in infection biology, cellular biology, epigenetics and fundamental microbiology, and has been recognized by several international prizes. Pascale Cossart is a member of the deutsche Akademie der Wissenschaften Leopoldina, the National Academy of Sciences, the National Academy of Medicine and the Royal Society.



Michel DELSENY

Member, Académie des sciences, France

Michel Delseny is CNRS emeritus director of research at the University of Perpignan (Via Domitia), where he has been director of the Genome and Plant Development Laboratory. His main research was on biology of seed formation and germination and he became interested in plant responses to abiotic stress. He contributed to the sequencing, to the functional analysis and to the understanding of the plant genomes evolution. He has been chief editor of the journals *Plant Science* and *Advances in Botanical Research*.



Bernard DUJON

Member, Académie des sciences, France

Bernard Dujon is emeritus professor at Pierre et Marie Curie University and Pasteur Institute. His research has mainly focused on genomes and the molecular mechanisms of their dynamic and their evolution. It was from yeast mitochondria that he discovered the first homing endonuclease, which laid the foundations for site-specific genome engineering. He is also member of the *Academia Europaea* and EMBO.

With the contribution of

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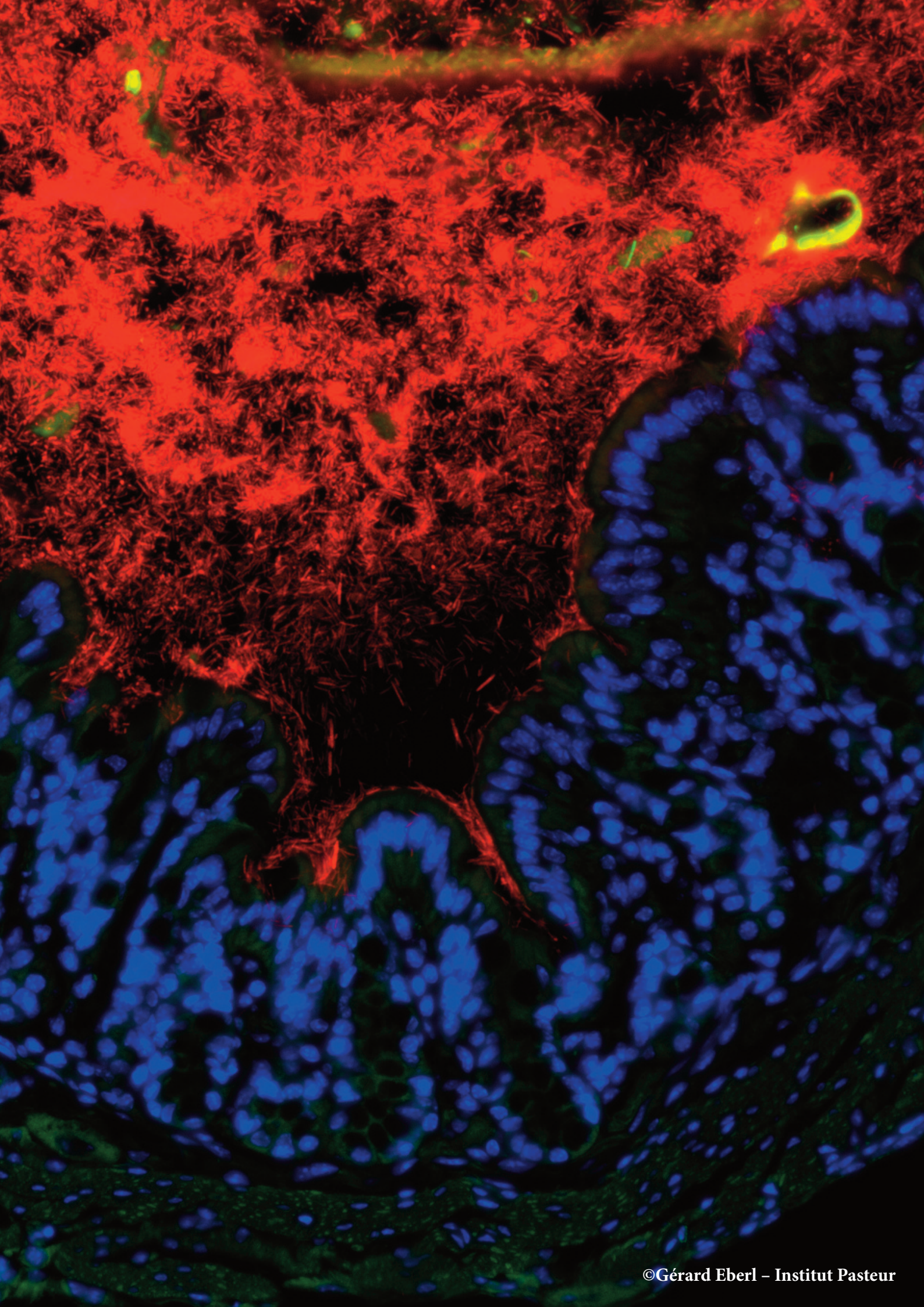


Érik ORSENNA

Economist, writer, member of the Académie française

Erik Orsenna is an economist by profession. He was cultural advisor to President Mitterrand and sat on the Conseil d'État (the highest legal authority in France). He is also a novelist, having written *The colonial exhibiton* (winner of the Goncourt prize in 1988), *The indian venture* or *The origin of our loves*.

Since 1998 he has been a member of the Académie française. As a specialist in raw materials, Erik Orsenna has been exploring the planet for the last fifteen years and has published a series of short summaries of globalization. After writing about cotton, water and paper, he authored *The geopolitics of the mosquito*, published by Fayard in March 2017.



P programme

- 9:30 Welcome address
Sébastien CANDEL, President, Académie des sciences, France
- 9:35 Opening address
Pascale COSSART, Secrétaire perpétuel, Académie des sciences, France

SESSION 1

*Chairpersons : Erik ORSENNA, Economist, writer, member of the Académie française
Michel DELSENY, Member, Académie des sciences, France*

- 9:45 How does an animal behave like a plant? Physiological and molecular adaptations of zooxanthellae and their host to symbiosis
Denis ALLEMAND, Scientific Director, Scientific Centre of Monaco, Monaco
- 10:15 Endosymbiosis as a source of immune innovation
Abdelaziz HEDDI, Professor, Institut national des sciences appliquées (INSA) Lyon, France
- 10:45 The use of *Wolbachia* to control the transmission of *Aedes aegypti* associated viruses :
The eliminate dengue program
Scott O'NEILL, Director, Institute of Vector-Borne Disease, Monash University, Australia
- 11:15 pause

Chairpersons : Michel DELSENY and Bernard DUJON, Members, Académie des sciences, France

- 11:45 How bacteria hijack plant development and attract insect vectors
Saskia HOGENHOUT, Professor, John Innes Center, United Kingdom
- 12:15 The honey bee gut microbiota - a versatile model for microbial symbiosis
Philipp ENGEL, Professor, University of Lausanne, Switzerland
- 12:45 Free lunch

SESSION 2

*Chairpersons : Pascale COSSART, Secrétaire perpétuel, Académie des sciences, France
Bernard DUJON, Member, Académie des sciences, France*

- 14:30 Bacterial interspecies quorum sensing in the mammalian gut microbiota
Karina XAVIER, Principal Investigator, Gulbenkian Institute of Science, Portugal
- 15:00 Regulation of inflammation by intestinal microbiota
Gérard ÉBERL, Professor, Pasteur Institute, France
- 15:30 From commensals to oncomicrobiotics
Laurence ZITVOGEL, Professor, Université Paris XI, Institut Gustave Roussy, France
- 16:00 Microbes and colon cancer: guilty or not guilty ?
Philippe SANSONETTI, Member, Académie des sciences, Professor, Collège de France, Professor, Pasteur Institute, France
- 16:30 General discussion and conclusion
Pascale COSSART, Secrétaire perpétuel, Académie des sciences, France
Michel DELSENY, Member, Académie des sciences, France
Bernard DUJON, Member, Académie des sciences, France

Biographies and abstracts



Denis ALLEMAND

Scientific Director, Scientific Centre of Monaco, Monaco

Denis Allemand is the Scientific Director of the Scientific Centre of Monaco and Professor of Biology at the University of Nice-Sophia Antipolis. He received his PhD in pharmacological science and endocrinology at the University of Montpellier II (France) in 1986. His main area of research is related to comparative and conservation physiology of marine organisms such as Cnidarians with an emphasis on two major biological functions: biomineralization and symbiosis. He co-authored over 140 research articles.

How does an animal behave like a plant? Physiological and molecular adaptations of zooxanthellae and their host to symbiosis

Cnidarians (corals and sea anemones) harboring photosynthetic microalgae derive several benefits from their association. In order to allow this association, numerous symbiotic-dependent adaptations in both partners, resulting from evolutionary pressures, have been selected.

The Dinoflagellate symbionts (zooxanthellae) are located inside a vesicle in the Cnidarian host cell and are therefore exposed to a very different environment compared to the free-living state of these microalgae in term of ion concentration and carbon content and speciation. In addition, this intracellular localization imposes that they rely completely upon the host for their nutrient supply (nitrogen, CO₂). Symbiotic-dependent adaptations imposed to the animal host by the phototrophic symbiosis are more relevant to photosynthetic organisms than to metazoans: indeed the cnidarian host often harbors diurnal change of morphology in order to adapt itself to the amount of light and possesses carbon-concentrating mechanisms, antioxidative defences and UV sunscreens similar to that present in phototrophs. These adaptations will be discussed from an ecological and evolutionary point of view.



Abdelaziz HEDDI

Professor, INSA Lyon, France

Abdelaziz Heddi has defended his thesis on insect symbiosis at INSA Lyon on 1990 under the supervision of Pr Paul Nardon. He has then experienced post-doctoral fellowships with Dr Patrick Lestienne and Dr Georges Stepien at the CHR of Angers, and with Pr Douglas Wallace at Emory school of medicine at Atlanta, where he entered new research area on human genetic diseases. He joined on 1994 the BF2i Lab (UMR INRA/INSA de Lyon 203). He established on 1998 a new team on « Symbiosis & Immune Signaling » dealing with host-symbiont molecular dialogue, and he is leading the BF2i Lab since 2012.

Endosymbiosis as a source of immune innovation

Many insects sustain long-term relationships with intracellular symbiotic bacteria (endosymbionts) that provide them with essential nutrients. While it is well documented that endosymbionts experience a drastic genome shrinkage that results in the loss of bacterial virulence genes, whether and how the host immune system evolves towards the tolerance and control of bacterial partners remains questionable. We have shown that insects have selected a « compartmentalization strategy » that consists in secluding endosymbionts within specialized host cells, the bacteriocytes, thus preventing direct symbiont contact with the host systemic immune system. I will address recent advances at the understanding of the bacteriocyte immune regulations involved in endosymbiont maintenance and control. I will discuss how insects track endosymbiont dynamics through at least two mechanisms: i- Immune effectors that target endosymbiont cell division and help to maintain a homeostatic state within bacteriocytes, and ii- cellular processes such as apoptosis and autophagy, that adjust endosymbiont load to the host developmental requirements, hence ensuring a fine-tuned integration of symbiosis costs and benefits.

Scott O'NEILL

Director, Institute of Vector-Borne Disease, Monash University, Australia

Scott O'Neill leads *The eliminate dengue program*, an international research collaboration which aims to reduce the global burden of mosquito-borne disease. His team is implementing a sustainable control method using *Wolbachia* to reduce the ability of *Aedes aegypti* mosquitoes to transmit harmful viruses including dengue and Zika. The program is now expanding and preparing for efficacy trials and large pilot deployments in a number of countries around the world. Scott O'Neill has received many awards including the Centenary Medal, the Mackerras Medal and is a Fellow of the Australia Academy of Science, the American Association for the Advancement of Science and the American Academy of Microbiology. He is now the Director of the Institute of Vector-Borne Disease at the Monash University .



The use of *Wolbachia* to control the transmission of *Aedes aegypti* associated viruses : *The eliminate dengue program*

Our group is examining the potential use of inherited bacterial symbionts of insects known as *Wolbachia* as a novel method to interfere with *Aedes aegypti* associated viruses. This work has now progressed from basic bench studies into open field trials in five countries. I will give an overview of *Wolbachia*-mosquito-pathogen interactions as well as the current status of the global eliminate dengue program that aims to deploy *Wolbachia* infections as a cost effective and sustainable approach to control *Aedes aegypti* associated viruses.

Saskia HOGENHOUT

Professor, John Innes Center, United Kingdom

The research of Saskia A. Hogenhout (Dep. Crop Genetics, John Innes Centre (JIC), Norwich, UK) focuses on the molecular basis of plant-microbe-insect interactions. Saskia Hogenhout obtained her MSc at Vrije University Amsterdam, Netherlands in 1994 and her PhD at Wageningen University, Netherlands, in 1999. She started her own group as Assistant Professor at The Ohio State University, USA, in 1999 and received tenure and became Associate Professor in 2005. Saskia Hogenhout moved her research group to the JIC in June 2007. She is Honorary Professor at University of East Anglia, Norwich, UK, since 2013.



How bacteria hijack plant development and attract insect vectors

Phytoplasmas are obligate bacterial parasites that inhabit the vascular tissues of plants and are transmitted by sap-feeding insect vectors. These parasites induce dramatic changes in plant development, including proliferation of stems (witch's brooms) and the reversion of flowers into leaf-like structures (phyllody). My group has shown that phytoplasmas generate these disease symptoms via the production of an arsenal of virulence proteins, named SAPs, which interact with and promote the degradation of a diverse range of plant transcription factors, including homeodomain proteins. Interestingly, these SAPs also convert plants into more attractive hosts for feeding and egg laying by phytoplasma insect vectors. Thus, phytoplasma virulence proteins have evolved to interfere with key plant developmental processes and simultaneously promote the fitness of sap-feeding insect vectors on which phytoplasmas depend for spread in nature.



Philipp ENGEL
Professor, University of Lausanne, Switzerland

Philipp Engel carried out his doctoral research at the University of Basel, Switzerland, studying the bacterial pathogen *Bartonella* with a focus on Type IV secretion systems, host adaptation and bacterial genomics. For his postdoc, he then moved to Yale University to the group of Prof. Nancy Moran where he started to work on the gut microbiota of honey bees to understand genomic and functional aspects of microbial symbiosis. In 2014, Philipp Engel became an Assistant Professor at the University of Lausanne, Switzerland. His lab uses the honey bee microbiota as a model to study gut microbiology and symbiosis.

The honey bee gut microbiota - a versatile model for microbial symbiosis

Gut microbial communities are important determinants of animal health. However, their complex composition displays a formidable challenge for understanding gut symbiosis. The honey bee, *Apis mellifera*, harbors a surprisingly simple yet conserved bacterial community in its intestine ideal to be used as a model to study fundamental principles of gut microbiota function and evolution. In my talk, I will give an overview of our current understanding of the honey bee gut microbiota and highlight a few research projects running in my laboratory. The main focus will be on a recent nontargeted metabolomics study that enabled us to identify metabolic changes induced by the gut microbiota and to disentangle the contributions of individual community members. Our results reflect the longstanding evolution of this bacterial community with its social bee host, revealing adaptation to the host's diet and occupation of distinct metabolic niches in the gut.



Karina XAVIER
Principal Investigator, Gulbenkian Institute of Science, Portugal

Karina Xavier is Principal Investigator at Instituto Gulbenkian de Ciência in Portugal since 2006. The main focus of her research is inter-species cell-cell communication in bacteria and its role in beneficial and hostile interactions with the host. She received her PhD from ITQB – Nova, Lisbon in 1999 for her work on metabolism of carbohydrates in Archaea. She started working on bacterial quorum sensing in her postdoc at Princeton University. She showed that the quorum sensing signal autoinducer-2 can foster interspecies communication in bacteria and recently her group showed that manipulation of interspecies quorum sensing in the mammalian gut can influence species composition of the microbiota.

Bacterial interspecies quorum sensing in the mammalian gut microbiota

The mammalian gastrointestinal tract harbours a diverse and complex resident bacterial community, which interacts with the host in many beneficial processes required for optimal host health. We are studying the importance of bacterial cell-cell communication mediated by the interspecies quorum sensing signal AI-2 in the beneficial properties of the gut microbiota. Our recent work provided the first evidence that AI-2 produced by *Escherichia coli* can influence the species composition of this community in the mouse gut. We showed that, under conditions of microbiota imbalances induced by antibiotic treatments, *E. coli* that increases intestinal AI-2 levels not only had an effect on the overall structure of the microbiota community but specifically favored the expansion of the Firmicutes phylum. Because the Firmicutes are very important for many gut functions, and were the group of bacteria most severely affected by antibiotic treatment with streptomycin, we are addressing the possibility that AI-2 can influence the balance of the major bacterial groups in the gut and promote recovery of gut homeostasis. Overall, we want to understand how bacterial chemical signaling shapes the multi-species bacterial communities in the mammalian gut and how these communities affect host physiology.

G rard EBERL

Professor, Pasteur Institute, France

G rard Eberl did his PhD at the University of Lausanne studying the structure of T cells epitopes, before moving for a first postdoc to the Ludwig Institute on Cancer Research, studying the development and function of invariant NKT cells. A second postdoc in New York lead him to characterize the role of the nuclear hormone receptor ROR t in innate lymphoid cells. In 2005, G rard Eberl was recruited to the Pasteur Institute in Paris to lead the Lymphoid Tissue Development Unit, which became the Microenvironment & Immunity Unit in 2015. Since now 10 years, his lab is studying the impact of the symbiotic microbiota on the development and activity of the immune system, primarily in the intestine, but also at more distant sites, such as adipose tissue and lung. More recently, he became interested in understanding how the microbiota can also influence the behaviour of mice through the activation of the innate immune system. Since 2015, G rard Eberl is chair of the department of Immunology.



Regulation of inflammation by intestinal microbiota

The symbiotic microbiota represses the development of allergic inflammation, but the mechanisms involved are unclear. We have shown that intestinal bacteria induce the generation of type 3 T cells (Th17 cells and associated Tregs) that directly regulate pro-allergic type 2 T cells. In the absence of type 3 T cells, anti-helminth, but also pro-allergic responses, are exacerbated. Furthermore, the absence of microbiota during weaning has similar consequences on the deregulation of the immune system that last until adulthood, a phenomenon we name “imprinting”. We propose a model of the immune system where different types of competing and mutually suppressive responses establish a healthy equilibrium. When this equilibrium is lost, because of an absence of one type of microbe in the environment, inflammatory pathology develops. Therapeutic strategies can be designed with the aim to restore immune equilibrium to counter immunopathology.

Laurence ZITVOGEL

Professor, Universit  Paris XI, Institut Gustave Roussy, France

Laurence Zitvogel, MD (clinical oncology), PhD (tumor immunology), PU-PH University Paris Saclay (Clinical Biology), graduated in Medical Oncology in 1992. She started her scientific career at the University of Pittsburgh (USA) in 1993. She became Research Director at INSERM and scientific director of the Immunology program at Gustave Roussy. She is a French pioneer in the field of tumor immunology and cancer immunotherapy. She unraveled two concepts, i) the immunogenic cell death ii) the oncomicrobiotics for cancer immunosurveillance. She was the recipient of many awards (including Translation Research INSERM Prize and the Brupbacher Award).



From commensals to oncomicrobiotics

The tumor microenvironment is influenced by anticancer therapies which affect the gut homeostasis. A deviated repertoire of the intestinal microbiome called « dysbiosis », caused by broad spectrum antibiotics compromised the efficacy of cyclophosphamide (CTX), an immunomodulatory alkylating agent exerting cytotoxic effects against cancer. Similarly, the gut microbiota boosts the efficacy of ipilimumab, a mAb targeting CTLA-4. Mechanistically, CTX is responsible for disrupting the gut barrier integrity as well as intestinal homeostasis, allowing a NOD1/2-dependent translocation of Gram⁺ bacteria into secondary lymphoid organs. *Enterococcus hirae*, which modulates systemic immunity through the elicitation of bacterial-specific Th1 and pathogenic Th17 cells, also induced tumor-specific CD4⁺ and CD8⁺ T cell responses. Finally, *E. hirae* specific-memory Th1 immune responses selectively predicted longer progression-free survival in advanced lung or ovarian cancer patients treated with immunotherapy and chemotherapy. Altogether, *E. hirae* represents a valuable probiotic against cancer. Other oncomicrobiotics discovered in the context of CTX, CTLA4 and PD1 blockade will be presented at this meeting.

