Philippe Sansonetti
Biosketch

Sansonetti pioneered cellular microbiology by designing a novel multidisciplinary framework to decipher the complex molecular cross-talks engaged between the invasive bacterium *Shigella* and its host, supporting the occurrence of dysentery. With his group, he achieved ground-breaking contributions encompassing a unique combination of basic, applied, and clinical research, and capitalizing on his deciphering of the strategies used by *Shigella* to escape host immune responses, he could identify essential intracellular molecules and pathways sensing and responding to pathogens.

Contributions in basic research:
Sansonetti established *Shigella* as a unique model to study invasive pathogens. By discovering the *Shigella* virulence plasmid encoding cell invasion via a Type III secretion system (T3SS) and its dedicated effectors (1-9), and by providing the first exhaustive identification of the genetic sequences (plasmid and chromosome) allowing this invasive pathogen to disrupt and invade the intestinal epithelium (10, 11) (12-14). He developed cell assay systems that led to discovery and characterization of key phenotypes like actin-dependent bacterial entry into epithelial cells and bacterial escape into the cytosol (15, 16), followed by actin-dependent intracellular motility and cell-to-cell spread (17, 18). In the following years, he deciphered the fine molecular signals leading to actin assembly, organization and disassembly supporting the dynamics of bacterial entry foci and cytosolic motility (19-36). He also identified essential mechanisms linking inflammatory destruction of the epithelium to development of the invasive process, i.e. he was the first to discover a caspase-1-dependent, proinflammatory apoptosis process of macrophages triggered by invasive *Shigella*, a prelude to pyroptosis and the inflammasome (37-42), and to describe the pro-inflammatory reprogramming of epithelial cells themselves, also linked to expression of the *Shigella* invasive phenotype (43). He eventually provided a unique integrative view of infection, *in vitro* and *in vivo* (44), leading to better understanding how the host senses the bacterial danger and how the pathogen uses and subverts innate immune responses to respectively disrupt the epithelial barrier and survive humoral and cellular immune effectors (45-50). This succession of original discoveries set the basis of the novel model of interdisciplinary study of infections called “cellular microbiology”.

In the past twenty years, they have unraveled several novel concepts:
- Intracellular sensing of bacteria, leading to the discovery of Nod molecules as cytosolic sensors, and bacterial muropeptides as their proinflammatory agonists (51-53).
- Identification and analysis of a battery of T3SS effectors regulating host responses by post-translational modifications (i.e. phosphorylation, dephosphorylation, ubiquitylation) of molecules in the NF-κB and MAP-Kinase pathways, engaging genetic and epigenetic repression of innate immunity gene expression (54-58). His group showed that transcription of the plasmid genes encoding these effectors (i.e. *ospG*, *ospF* and several *ipaH* genes) is under the control of T3SS activation sensing via MxiE, a transcriptional activator (59). In addition, we could also show that *Shigella* has developed capacities to subvert essential mechanisms of cell homeostasis such as sumoylation (60) and autophagy (61, 62).
- Subversion of cellular mechanisms of secretion by *Shigella*, involving Golgi disruption and receptor recycling arrest (63), and demonstration, with *Salmonella*, of the essential role of villin in engaging disruption of the apical epithelial brush border in preparation of entry (64).
- Manipulation of connexin-based hemichannel functions of ATP secretion modulating cell surface dynamics and strongly repressing danger signals that warn the host of epithelial engagement by a pathogen (65). However, beyond their initial demonstration that *Shigella* strongly affects innate immune responses, including expression of epithelial antimicrobial peptides (66), thereby increasing its survival chances in front of inflammation caused by its invasive phenotype, they showed that *Shigella* also subverted adaptive immunity by engaging effector cells such as T and B lymphocytes.

- Blocking of T-cell migration by hydrolysis of PI(4,5)P2 (67, 68) and apoptotic killing of B cells by a secreted effector, IpaD (69), both contributing to *Shigella* creating a strong immunosuppressive environment (70). These studies have led to the « kiss and run » concept whereby S*higella* engages and injects T3SS effectors into lymphocytes without getting into the dead end of cellular invasion, thereby amplifying its immunosuppressive capacity (71).
- In the more recent years, Sansonetti also engaged in identifying the environmental conditions faced by *Shigella* when reaching the gut epithelial surface and developed elegant reporter strains to explore these conditions and how the bacteria adapt accordingly. This led, for instance, to the recognition of the presence of oxygen at the epithelial surface and the major role plaid by Fnr, the bacterial sensor of oxygen tension in regulating the function of the T3SS (72). By engineering a reporter strain in which expression of a fast-folding/fast quenching GFP was put under the control of a mxiE-sensitive promoter that is active only upon activation of the T3SS, he could demonstrate that the T3SS was functional only during the phases of engagement of the plasma membrane for entry and cell-to-cell spread (73).
- More recently, he developed an innovative method combining global analysis of *Shigella* infection foci in the Guinea pig colon, a model that he showed is susceptible to shigellosis. By combining tiled confocal imaging of the colonic tissue with “machine learning” and big data management, they demonstrated that *Shigella* primarily invades the epithelial crypt (74), a key structure that accounts for epithelial regeneration. They also demonstrated that *Shigella sonnei* harbors and uses a Type 6 secretory system (T6SS) that allows its ecological substitution to the expense of resident *Escherichia coli*. A clear demonstration that subversion of the microbiota is an obligatory first step of colonisation/invasion of the mucosal surface for a pathogen (75). These successive discoveries represent a true “second breath” of *Shigella* research and are of more global value in the study of bacterial pathogenesis, leading to the renewed concept of “cellular microecology”.

Shigella vaccine development:
Sansonetti was first to develop a vaccine against shigellosis by rational genetic attenuation of virulence based upon the knowledge his group had accumulated on the genetic bases of cell and tissue invasion (76). These candidate vaccines have successfully gone through phase 1 and 2 clinical trials in USA, UK and France (77-82). In 2009, he was successful in being awarded the coordination of a major European-Union funded grant (12 million Euros) - STOPENTERICS - to hasten the conception and clinical development of a novel generation of vaccines against Enterotoxigenic *Escherichia coli* (ETEC) and *Shigella,* the two major causes of severe enteric infections in the developing world. Following this program, a novel prototype of conjugate vaccine in which the somatic/serotype specific O-polysaccharides are chemically synthesized (83, 84) has now completed a phase 1 trial at Tel Aviv University Vaccine Center (85), showed strong immunogenicity to such a level that the Bill and Melinda Gates has decided to fund its completion (4 serotypes) and the necessary future clinical trials: a challenge study is on its way as well as a large phase II study in sub-Saharan Africa.

Gut microbiome, from homeostasis to disease:
In the past 12 years, thanks to the support of the Howard Hughes Medical Institute and the successive award of two prestigious European Council (ERC) Advanced grants respectively called HOMEOEPITH and DECRYPT, Sansonetti started to tackle the field of bacterial symbiosis, with the aim of switching it from descriptive metagenomics to a true mechanistic “cellular microbiology of symbiosis”, capitalizing on their work on pathogens to identify the molecular cross-talks achieving symbiotic/mutualistic interactions between the gut mucosa and the microbiome - “from metagenomics to experimentomics”- particularly how bacteria of the gut microbiome regulate epithelial homeostasis.
They have developed essential tools, such as exhaustive mutant libraries, and entered the field of “culturomics” to be able to functionally analyze uncultivable microbes. Here are two examples:
- Global mutagenesis of the genome of a *bona fide* symbiont, *Lactobacillus casei*, thereby providing the first genome-wide functional analysis of a symbiont’s colonization of the gut (86).

- Breakthrough development of a technique of *in vitro* growth of the pathobiont “segmented filamentous bacterium” (SFB), a pioneer gut colonizer that primes the maturation of the gut mucosal immune system (87).

He also demonstrated essential/original basic mechanisms governing maintenance of the gut-microbiota homeostasis such as:

- Unraveled an epigenetic mode of regulation controlling the expression of antimicrobial peptides that are potent regulators of the microbiota balance. This discovery opens the way to use epigenetic pharmacology to explore the capacity to enhance epithelial antimicrobial peptides expression in circumstances requiring increased protection at the mucosal surface (88).
- He was also first to show that muramyl-dipeptide (MDP) and peptidoglycan from the microbiota exert a potent cytoprotective effect upon gut stem cells which express a high level of Nod2, the cytosolic receptor for MDP submitted to cytotoxic/genotoxic stress (89). This breakthrough discovery opens the way to better understanding of the role of the microbiota in regulating epithelial regeneration. It also opens a novel angle to the pathogenesis of Crohn’s disease that may be more of a pathology of delayed epithelial repair following an injury (90). A recent contribution of his group illuminated the cytoprotective mechanism by demonstrating that axtivation of the Nod2 cascade in stem cells elicited autophagy/mitophagy, hence protecting stem cells against the deleterious effect of oxygen radicals produced under genotoxic stress (91).
- By combining LASER-capture microdissection on murine cecal and colonic tissue sections, DNA extraction, pyrosequencing and 16S metataxinomics, Sansonetti identified a “crypt-specific core microbiota” dominated by a set strictly aerobic, non-fermentative bacterial genus belonging in large majority to *Acinetobacter*, *Delftia* and *Stenotrophomonas* genera (92). They were able to grow these microorganisms and confirmed their presence in the cecal/colonic crypts in wild rodents, thereby eliminating a breeding bias. They demonstrated that endotoxins from CSCM members were the dominant crypt bacterial agonists causing necroptosis of stem cells and progenitor/proliferative cells, and accelerated differentiation of mature/non-cycling cells (93). On these bases, He proposed a theory according to which a limited set of environmental bacteria have been engaged by co-evolution in a potent symbiotic interaction that regulates epithelial proliferation/differentiation and protects the intestinal crypt against microbial and genotoxic aggressions.

This innovative work has implications in the regulation of epithelial development and repair – particularly following cytotoxic stress - and addresses issues such as chronic intestinal inflammation and rupture of the epithelial barrier in conditions of imbalanced diet, *i.e.* high fat diet leading to quick and major combination of gut dysbiosis and collapse of epithelial impermeability (94). This work is also relevant to the pathogenesis of colorectal cancer which appears to involve the combination of a dysbiosis and the excessive presence of certain pathobionts like *Streptococcus gallolyticus* whose overgrowth capacity is explained by its production of a colicin that causes its ecological substitution to the expense of enterococci and other firmicutes in conditions of high concentration of secondary bile salts that is caused by the oncogenic environment (95). This is a novel angle in studies of the host-microbe relationship.

Sansonetti’s more recent work has progressed in defining the dysbiosis accompanying the development of colorectal cancer in humans. They have shown that upon transplantation to mice, samples of dysbiotic stools from CRC patients caused crypt aberrations and epigenetic modifications corresponding to hypo/hyper methylation in promoters of tumor suppressor and oncogenic genes similar to those observed in patients. A cellular microbiology of CRC is on its way (96).

- Last but not least, they have shown an important role plaid by the microbiota in controlling absorption of micelled alimentary lipids. Major bacterial effectors accounting for the control of lipid absorption have been identified (97). This work has possible implications in infant nutrition, considering the high concentration of lipids in maternal milk, and in adults to better control cardiovascular risk in relation to the qualitative and quantitative parameters of absorbed lipids.

Translational research:
On these bases, in addition to our vaccine programs, we develop several translational projects such as:
- A discovery program of molecules stimulating the expression of epithelial antimicrobial peptides. As above-mentioned, our recent evidence indicate that induction of antimicrobial peptides expression is strongly controlled by epigenetic mechanisms that are relaxed by epigenetic drugs such as HDAC inhibitors (88).
- A parallel clinical study on gut bacterial translocation in leukemic patients in bone marrow aplasia following chemotherapy and how it relates to the bactericidal role of antimicrobial peptides. Such patients would be candidates for therapeutic strategies enhancing barriers protection by inducing high levels of antimicrobial peptides (Wyplosz et al. manuscript in preparation).

Sansonetti has also completed an ambitious study of the pathogenesis of child stunting and associated Pediatric Environmental Enteropathy (PEE) in sub-Saharan Africa (Central African Republic and Madagascar). It is the first etiology of malnutrition in infants in low-income areas and responds to small intestinal overgrowth (SIBO) of a dysbiotic microbiota whose composition is unknown. This dysbiosis is considered responsible for low-grade chronic mucosal inflammation and intestinal atrophy that reduces digestive and absorptive capacities in the duodeno-jejunum. Their study –MICROBIOTA – was largely aimed at identifying the composition of this dysbiosis and, in this basis, disentangle the pathogenesis of PEE and offer biomarkers for early detection, as well as preventive and therapeutic solutions to eliminate stunting and psychomotor retardation that are the dominant consequences of PEE. Their results show massive proliferation of oro-pharyngeal bacterial taxa in the duodenum and a signature of this dysbiosis of the upper intestinal tract can be found in the feces in comparison with matched non-stunted children (98).

In summary, Sansonetti has made outstanding basic discoveries that have forged the multidisciplinary field of microbial pathogenesis, while also developing translational research programs largely aimed at improving health of children in the most impoverished areas of the planet, well in line with the Pasteurian tradition.

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