Laudatio for Prof. Dr. Alberto Mantovani

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Professor Alberto Mantovani is an oustanding pioneer of cytokine research, which began to coalesce as a distinct field in the early 1980s. At that time, the hypothesis that cells must communicate with one another in response to environmental changes such as infection, tumor growth, or normal development led to the search for factors beyond those discovered through classical research in endocrinology. The low abundance of cytokines and their pleotropic effects were enormous challenges during the early years of the field, when protein separation methods alone allowed the identification of several of these crucial factors. Fortunately, by the mid-1980s, the explosion of molecular cloning technology greatly accelerated cytokine research. Alberto Mantovani was at the vanguard of this research and began asking how the cellular environment of a tumor influences macrophage function, and vice versa. He focused his attention on these tumor-associated macrophages (or TAMs, an acronym he coined in 1978) which, as he noted, are the principal host inflammatory cells in most tumors. He proposed that TAMs exert a pro-tumor function by favoring neoplastic cell growth and progression to higher states of transformation. This concept ran contrary to the accepted views of the time, which held that immune cells must inhibit tumor growth. However, the fact that inflammatory cells and mediators are key components of a pro-tumor microenvironment is now generally accepted. This realization was long in coming. Key evidence in support of the new view was provided by Mantovani himself, who discovered the activation of endothelial cells and the promotion of metastasis by inflammatory cytokines. At present, diagnostic and therapeutic efforts aimed at targeting TAMs are well developed, and Mantovani recently demonstrated that targeting tumor-promoting TAMs can be beneficial in human cancer. He ultimately established a model of macrophages M1-M2/M2-like as extremes among TAMs in a spectrum of activation states, which has had a profound impact in the field of innate immunity, extending beyond cancer.

Mantovani's early studies of the origin of macrophages infiltrating tumors led him to describe the chemokine *« monocyte chemotactic protein-1 »* (MCP-1; now called CCL2) as a tumor-derived chemotactic factor active on monocytes but not on neutrophils, This discovery was followed by its molecular identification in association with Jo Van Damme. Mantovani's contribution to the

birth and development of the chemokine field was pre-eminent and is recognized as such by his peers.

Alberto Mantovani and coworkers further showed that chemokines act on dendritic cells and orchestrate dendritic cell trafficking. Their analyses revealed that chemokines differentially affect polarized Th1 and Th2 populations, and that chemokines encoded by the oncogenic virus HHV8 (involved in Kaposi's sarcoma and hematological neoplasias) preferentially attract Th2 and T regulatory cells. These studies thus identified a novel pathway for subversion and diversion of effective anti-viral/anti-tumor immunity. The contemporaneous observation that chemokine receptors are differentially expressed in T cell types has had a major impact in immunology.

Maintaining his focus on genetic and molecular links between human cancer and inflammation, Mantovani discovered that the chemokine receptor CXCR4, frequently upregulated in cancer, is controlled by the HIF-von Hippel Lindau pathway. Moreover, in collaboration with Dr Pierotti, A. Mantovani linked a common cancer-causing genetic anomaly in humans, that is the RET-PTC rearrangement, to activation of a distinct proinflammatory program *in vitro* and *in vivo*.

Dr. Mantovani also made seminal contributions to the general field of inflammatory cytokines. He identified the type II interleukin-1 (IL-1) receptor as a decoy receptor, i.e., a molecular trap for the agonist which can inhibit signaling in a dominant manner. This discovery of a decoy receptor was without precedent in biology and represented a paradigm shift in the face of the original classical definition of “receptor” by Langley in the first half of the 20th century, which includes ligand recognition and signalling. It is now apparent that decoy receptors are widely employed to regulate the action of cytokines, chemokines and growth factors.

Alberto Mantovani was also the first to describe the key role of the adaptor MyD88 in signaling by TLR4, and he also defined key elements of the TLR signaling cascade. This ground-breaking study paved the way to the subsequent dissection of the role of the MyD88 pathway in TLR signaling and in IL-1 signaling in innate immunity, inflammation and cancer. By itself, it represented a major body of work. Mantovani went on to discover negative regulators of these signaling pathways and together with his group cloned and characterized the TIR8/SIGIRR molecule (also called IL-1R8) now known as an essential regulator of inflammation and inflammation-associated cancer.

More recently, while pursuing and extending their interests in innate immunity, Alberto

Mantovani and his group cloned the first long pentraxin, PTX3, a distant relative of the C Reactive Protein. They showed that PTX3 acts as a prototypic circulating innate immunity recognition protein, which proved to be essential for resistance to selected microbial pathogens. One of these, *Aspergillus fumigatus*, represents a formidable threat to cancer patients, particularly after bone marrow transplantation. Mantovani's efforts on this molecule encompass in addition to its discovery and cloning, the structural immunobiology of PTX3 and its use as a novel diagnostic and therapeutic tool. These studies highlighted in particular that PTX3 genetic constitution is a major risk factor for Aspergillus infection and may pave the way to therapeutic exploitation in a Precision Medicine context.

For several years now, bibliometric analyses have indicated that Alberto Mantovani is the most quoted Italian scientist and one of the 10 most quoted immunologists worldwide. His work had been cited more than 70,000 times to this date. His discoveries over the past forty years have set new standards in the fields of innate immunity, inflammation, and tumor immunology, and have led to entirely new concepts.

In spite of his stellar contributions to basic science and in particular to immunology, Alberto Mantovani has remained close to patients and to health problems – his objective has always been to alleviate suffrances and to help preventing the spread of diseases among the human populations. Alberto Mantovani has a broad understanding of culture and society and a deep feeling for human distress. He is humanist and a benefactor for his fellow citizens – he is also in a true sense a gentleman.

We are happy and proud to honor him today with the Robert Koch Prize.