

In Memoriam



Pierre Youinou, MD, DSc
1945-2022

On August 26th, 2022, the choir of the immortals, founders in the field of immunopathology of autoimmune rheumatic diseases, was joined by Pierre Youinou.

Pierre Youinou received his MD with honours from the University of Brest in 1976 and his DSc from the University of Paris VI in 1984. During his introductory course in immunology, he was marked by two famous names: Professor Maxime Seligman (1976-1977) and Professor Ivan Roitt (1981-1983). He was nominated professor of immunology at the University of Brest, France in 1985. Head of the hospital immunology department at Brest Medical School from 1989 to 2011, he obtained recognition for this department as a European reference laboratory in autoimmunity.

His research laboratory “Immunology and Pathology”, which he created in 1983 and lead until 2011, is studying the role of B cells in the pathogenesis of primary Sjögren’s syndrome (pSS), as well as certain clinical, immunological and pathological aspects related to autoimmune diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Professors of the Brest Medical Center in internal medicine, rheumatology, haematology, nephrology, odontology, influenced and attracted by his infectious enthusiasm, his sense of leadership and his deep knowledge in immunology, adopted and followed with great pleasure the clinico-laboratory protocols he was setting-up in order to study the different clinical and biological aspects of autoimmune diseases.

Pierre has written more than 700 scientific articles, and among them 200 book chapters, editorials and reviews with great recognition by his peers as evidenced by the numerous awards he has received. Among them, the Eloi-Collery Prize from the French National Academy of Medicine in 1997, the Brittany Research Prize in 2000, the Honorary Doctorate from the University of Bogotá, Colombia, in 2011 or the

title of “Master” from the American College of Rheumatology in 2015. He was invited to deliver lectures related to his research by many medical schools from all over the world and served on the Editorial boards of 40 different journals in Rheumatology, Internal Medicine and Immunology and realised more than 2000 expertises as a reviewer for manuscripts and grants.

In the early 80s, Pierre’s laboratory was one of two in Europe, along with the one directed by his friend Prof. Harry Moutsopoulos in Greece, to study the pathogenesis of Sjögren’s syndrome. His clinical research has provided important insights in the functions of B cells into autoimmune systemic and rheumatic disorders. From his early years in research, he dedicated himself to the study of normal and pathological B lymphocyte with application systemic autoimmune diseases. Pierre Youinou was assigned a project to characterise CD5⁻ positive B cells in autoimmune diseases. He established that CD5⁺ B cell subsets were extended in patients with RA and pSS and produced most of natural antibodies (Abs) and autoAbs. However, through his different publications, it appears that CD5⁺ B cells had not the “exclusive rights” to the production of pathogenic antibodies. Furthermore, they can act as efficient antigen presenting cells and in this way potentially process and present auto-antigens to autoreactive T cells. Paradoxically, in the lights of his findings of the modulation of B cell signaling by CD5, it appears that this molecule plays a crucial role in preventing autoimmunity and that aberrations of signalling through CD5 could therefore lead to autoimmune diseases. In 2005, his group discovered a new variant of the CD5 protein. This results from the insertion of a human endoretrovirus (HERV) upstream of the *cd5* gene. The known exon 1 was thus renamed exon 1A and the new exon 1 termed exon 1B. Should E1A be selected a full length form of the protein

is synthesised, transports the SHP1 phosphatase to the vicinity of the BCR and favours the development of anergy. Should it be E1B, a truncated form of CD5 is synthesised, lacking of leader peptide and consecutively retaining SHP1 in the cytoplasm. The absence of SHP1 near the BCR allows the release of autoAbs. He observed that E1B, like any HERV-derived gene sequence, is controlled by DNA methyl transferase 1 and that epigenetic modifications are responsible for the decrease in the expression of CD5 in B cells from patients with SLE.

Pierre Youinou was particularly interested in the study of B cells in pSS. For many years, T cells were considered as solely responsible for the destruction of epithelial cells, and B cells were only considered as Ab producing cells. Beyond the paradigm that T cells maintain strict control over B cells, it is now acknowledged that B cells also produce a flurry of cytokines. He demonstrated that the distribution of mature B cells in the peripheral blood of patients with pSS is different from that in patients with other autoimmune diseases and in normal control subjects and that this might provide a useful diagnostic tool. Thus, distribution was characterised by an accumulation of immature B cells and a decrease of memory B cells. He also described that B cells, in the tissue lesions, can be primed to differentiate into B effector (Be)1 and Be2 cells producing Th1 and Th2 cytokines, respectively. He also reported on the characterization of B cells of germinal center-like structures infiltrating the salivary glands of patients with pSS. His data indicated that, in salivary glands, a minority of B cell clusters represent genuine germinal center cells, while the majority manifest features of marginal zone-like B cells. Interestingly both types of B cell aggregates included auto-reactive B cells. Thus, he rather conceived pSS as a quintessential model for B cell-induced autoimmunity. Such a view opens novel prospects for treatment, and especially in B cell-ablative therapies. Pierre Youinou also explored the cytokine BAFF (for B cell activating factor belonging to the TNF family) in autoimmune diseases. He highlights the difficulties for BAFF quantification by ELISA showing that most of the commercial tests were unable to detect non-glycosylated forms of BAFF present in the serum.

Pierre also focused on the function of anti-Fc γ receptor antibodies and anti-endothelial cell antibodies (AECA). He showed their deleterious effects in three ways: activation, induction of apoptosis and cytotoxicity. Although the link between AECA targets and their effects was not well un-

derstood, he sought to identify the receptor involved in the induced-pathogenic signals of anti- β 2GPI Abs in anti-phospholipid syndrome. He characterised with his collaborators an interaction between TLR2 and β 2GPI and showed that inhibition of this receptor decreased endothelial cell activation via β 2GPI.

In addition, Pierre wanted to make “the Brest Immunology centre” internationally known. For this reason, he did not accept, despite numerous requests, to move his laboratory to Paris and he organised the famous annual meetings on autoimmunity (Breton Workshop on Autoimmunity) in Brest in which the most prominent worldwide autoimmunologists participated. In return, clinicians and researchers from around the globe, studying the different aspects of pSS, to honour Pierre’s scientific contributions, elected that he host and organise the 10th International Symposium on Sjögren’s Syndrome in Brest in 2009; which he executed with perfection, in particular by enabling the creation of the worldwide network of associations of patients suffering from pSS.

A couple weeks before he passed away, when I told him how grateful I was to him, he answered me “Breton peasants, shy, like us, do not say what they feel. Faithful, they know. Therefore, they rely on each other, but it’s implicit, we don’t need to say it.” Pierre was like that, a deeply faithful person, a true Breton as he liked to recall.

It is now undeniable that the contribution of Pierre Youinou to the field of autoimmunity is tremendous. At “the tip of the tips” of Brittany, he created the “top of the tops” of the school dedicated to the study of B cells in autoimmunity.

Finally, Pierre was a lover of opera and literature, an erudite man, in a hurry, curious, enthusiastic and passionate. Pierre left behind his wife, Véronique, the discreet mainstay of Pierre’s household and a talented painter and their four children: Damien, Blanche, Véronique and Pierre Jr as well as eleven grandchildren.

He will undoubtedly be missed by his family, friends, colleagues and students. We will all remember him.

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