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Short overview of career

At time of writing my PhD dissertation devoted to the allosteric regulation of an enzymatic activity, I was invited by Professor J.C. Heuson to develop a unit on Estrogen Receptor at the IJB (1970); the apparent parallelism between the subject of my investigation (ligands - induced stuctural changes of a protein for modulating its function) and the estrogenic activation of ER justified this proposal even, as chemist, I had almost no knowledge in endocrinology. In fact, the establishment by E.V. Jensen (Chicago) of a relationship between the detection of ER in breast cancer samples and the response to endocrine teatments was the mean reason of this recruiment: my experimental aptitude appeared especially accurate for the development of estrogen binding assays suitable for local cilinical purposes. This was the start of an academical life that maintained until my retirement in 2009. Of course, other topics related to ER (now ER alpha) were adressed, *i.e*. assessment of molecular heterogeneity of ER in terms of hormone dependence, relation between the turnover rate of ER and its ability to regulate gene expression and proliferation, structural analysis of ER binding sites for natural and synthetic modulators of activity, design of cytotoxic- linked estrogens, influence of calcium and calmodulin on ER – mediated processes…

The property of a synthetic peptide corresponding to a part of the calmodulin binding site of ER retained a peculiar attention at the end of my academical function. In MCF-7 breast cancer cell culture, this peptide (P295-T311; ERalpha 17p) was found to enhance proliferation or to provoke apoptosis whether the growth medium has been or not treated to remove ER activating molecules (DCC treatment). It also favors the expression of markers usually detected under estrogenic exposure as well as the proteosomal ER degradation. The finding of a peptide including the P295-T311 sequence of ER in media from estradiol - treated cells concured to the concept that the secretion of proteolysis prducts of the receptor, including the present one, may contribute to the action of the hormone. This putative secretion may also participate to

the emergence in human sera of natural IgGs able to induce estrogenic responses through an apparent direct interaction with ER. The existence of such antibodies (described at first at IJB by my colleague A. Borkowski with which I collaborated in the early 80') is now well estabished.

A primordal factor for the progression of this program has been a permanent seach for cooperations wich foreign groups (production and exchange of componds, laboratory visits, tutorial advises and lectures…). Four of these cooperations merits a peculiar mention for their long existence (more than 5 years). The first of them, devoted to tamoxifen and derivatives, was conducted in the 80s with A.B.Foster and M.Jarman (Institute of Cancer Research, Sutton, UK). The second one, run at the same time with G. Jaouen and A. Vessières, concerns organometallic derivatives of this antiestrogen as well as estradiol (Ecole Nationale Supérieure de Chimie de Paris de Chimie/Université P. et M. Curie (UPMC), Paris). Noteworthy, G.J. proposed my candidature for a status of *Professor Invité* at UPMC that helped me to iniate other long-term investigations, especially with Y. Jacquot for the study of peptidic modulators of ER activity, including ERalpha17p. Y.J. revealed a capacity of the latter to activate signal transduction pathways through interactions with the cellular membrane, a topic also adressed by E. Castanas and its team (University of Crete, Grece). Worthy of note, this group identfied specific ERalpha17p transcriptional signatures related the degree of breast cancer malignancy. On the other hand, among prominent investigators who spent a time in Brussels, I select E.V. Jensen who demonstrated with me the conformational stabibility of ER activated by a ligand when the latter is removed from its binding site. This property (reported at a CBT symposium held in 1993 in Huddinge, Sweden), which may be related to a post- activation step required for the onset of a biological response, was found to infuence the receptor turnover rate.

Being now retired I encourage colleagues to pursue such sudies, with a special emphasis for recent peptidic/immunological findings described here. It is my feeling that they may open new avenues in fundamental endocrinology. For that purpose, I also write of reviews with a complementary hope to restore some interest for unexplained findings and paradoxes, forgotten or ignored at present.

List of pubications (~300) registered on ResearchGate, Academia and PubMEd/NCBI