Editorial

Immunophilins, Protein Chemistry and Cell Biology of a Promising New Class of Drug Targets – Part I

The origin of the family of proteins known as *Immunophilins* can be traced back to the year 1969, when the first specific ligand was discovered. By that time, an employee of a pharmaceutical company took with him soil samples from the Alps as part of a program of the company to analyze the presence of microorganisms able to produce new compounds of pharmaceutical interest, in particular antibiotics [1]. From those samples was isolated a fungus (*Tolypocladium inflatum*) that shows the ability to prevent the growth of other fungi. The active principle was identified as a cyclic undecapeptide, cyclosporine A [2], and its chemical synthesis was then published [3]. The studies showed that cyclosporine A has immunosuppressive effect in various experimental models [4, 5], which provided an extraordinary advance on the tissue and organ transplantation field since it was born by the end of the XIX century. At the beginning of the 80's, cyclosporin A became a sort of miracle treatment to avoid organ rejection.

After the discovery of cyclosporine A as an effective immunosuppressant, several alternative treatments were also established, including a macrolide lactone derivate known as FK506 (also called tacrolimus o fujimycin), which was isolated from *Streptomyces tsukubaensis* and firstly described in 1987 [6-8]. It was reported that FK506 is also effective in a wide variety of models of experimental transplantation and autoimmunity. Therefore, in addition to its obvious clinical importance, the discovery of FK506 yielded new insights into the mechanisms underlying the activation of T cells and its use is likely to impart even more important scientific information. The third classic drug also able to exert significant immunosuppressive actions is rapamycin, a macrolide discovered as a product of the bacterium *Streptomyces hygroscopicus* in a soil sample from Easter Island [9-11]. Soon after the discovery of these three drugs, scientists focused their studies on the identification of their intracellular molecular targets, and defined a new family of proteins known as immunophilins.

Today, the immunophilin family has been subdivided into three main categories according to the type of ligand they recognize, i.e., cyclophilins or CyPs, when they bind cyclosporine A (brand names are Gengraf, Neoral, and Sandimmune)), FKBPs or FK506-binding proteins when the bind FK506 (trade names Prograf, Advagraf, and Protopic) and also rapamycin (brand name Rapamune), and a third additional and still not well characterized CsA- and FK506-binding proteins subfamily. The two most relevant functional properties of immunophilins are the chaperone activity and the peptidyl prolyl isomerase enzymatic activity, which results inhibited upon complexing with the immunosuppressive drug. Beyond the fact that immunophilins are the cellular targets of immunosuppressive drugs, they also play several cardinal roles in the biology of the cell, which comprises various and versatile actions ranging from chaperoning client proteins for proper folding to neurotrophic or antiapoptotic actions.

The primary aim of the articles published in the present hot topic of Current Molecular Pharmacology titled *Immunophilins, a promising class of drug targets for alternative therapies,* is to contribute to a better understanding of the properties and potential uses of this important family of proteins as novel pharmacological targets. Due to the length of the articles, this issue has been split into two parts. In the part I, the first article by David LeMaster and Griselda Hernandez from the Department of Biomedical Sciences, University at Albany, analyzes the conformational dynamics of the most evolutionary and structurally similar domains to the archetypical immunophilin FKBP12, i.e. the FK1 domains of FKBP51 and FKBP52 and the low molecular weight immunophilin FKBP12.6, with the purpose to elucidate the relevance of these domains in both the therapeutic design of specific drugs and for gaining insight into how these small domains might participate in the collective transitions that occur within the signalling complexes in which they function.

Xixi Feng, Sebstian Pomplun, and Felix Hausch from the Max-Planck Institute of Psychiatry of Munich summarize recent advances in the development of FKBP ligands, which resulted in the first highly selective ligand for FKBP51 such as SAFit2, which allowed the proof-of-concept in mice for FKBP51 inhibitors as potentially novel antidepressants. Finally, the authors discuss pending issues that need to be addressed for the further development of FKBP51-directed drugs.

Amaravadhi Harikishore and Ho Sup Yoon from The Nanyang Technological University of Singapore focused their article on the molecular characteristics of canonical and non-canonical immunophilin family members from human and *Plasmodium falciparum and P. vivax*, and also analyze recent progresses on immunophilin inhibitor development, as well as future perspectives on structure-based design of non-immunosuppressive immunophilin ligands with potential pharmacological activities against infectious diseases.

Mingming Tong and Yu Jiang from The University of Pittsburgh School of Medicine provide a general comprehensive outline for the structures and diverse functions of FKBPs found in mammalian cells, including their participation in processes such as cancer neuroregeneration, neurodegenerative diseases, cell development, apoptosis, signalling cascade pathways, calcium channel regulation, etc.

Thomas Ratajczak from The University of Western Australia, analyzes the relevance of immunophilins as members of the steroid receptor-Hsp90 heterocomplex, the discovery of immunophilins, structural properties, both Hsp90-dependent and Hsp90-independent biological actions, as well as it is discussed how these immunophilins become superb candidates for diverse drug-targeting approaches in several diseases.

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In the second part of this issue, M. Lagadari, S.A. De Leo, M.F. Camisay, M.D. Galigniana and A.G. Erlejman from The University of Buenos Aires describe a novel molecular mechanism of regulation for NF-κB signalling cascade by FKBP51 and FKBP52, and postulate that the antagonistic actions of these proteins may be responsible for the pleiotropic effects of NF-κB in different cell types and tissues according to the expression balance exhibited for both immunophilins.

Naihsuan Guy, Yenni Garcia, and Marc Cox from The University of Texas at El Paso postulate the development of FKBP52-specific small molecule inhibitors as a highly targeted strategy with potential for the treatment of any disease that is dependent on given functional steroid receptor signaling pathway. They discuss that the proline-rich loop overhanging the FKBP52 FK1 catalytic domain is a key interaction surface within the receptor-chaperone complex highly attractive for a therapeutic approach to disrupt FKBP52 regulation of receptor activity in steroid hormone receptor-dependent physiology and disease.

Gabriel Fries, Nils Gassen, Ulrike Schmidt, and Theo Rein from the the Max-Planck Institute of Psychiatry of Munich analyze FKBP51 polymorphisms as emerging factors involved in stress-related mental disorders, mostly based on the inhibitory action of this immunophilin on the glucocorticoid receptor activity in the nervous system. They analyze the regulation of the feedback loops that command the biological response due to the onset of stressing and traumatic stimuli, and the relation of these events with the development and treatment of major depression syndromes.

Anna D'Angelillo, Stefania Staibano, Maria Romano and Simona Romano from The Federico II University of Naples review recent literature related to the FK506-binding protein of 51-kDa in the mechanisms that switch the TGF-β from a tumor suppressor to a pro-metastatic invader in processes that enable cancer cells to disseminate from primary tumors and spread to distant locations, therefore acquiring resistance to therapy and self-renewal capability.

Paul Lavin and Margaret Mc Gee from The University College Dublin summarize current understanding of the role of cyclophilins in cancer by reviewing the function of these immunophilins during mammalian cell division and HIV-1 infection, and highlight common processes involving members of the ESCRT (Sorting Complex Required for Transport) machinery, and Rab GTPase protein families.

Finally, Lana McClements, Stephanie Annett, Anita Yakkundi and Tracy Robson from the School of Pharmacy, Queen's University Belfast, focus on the different roles of immunophilins as therapeutic and biomarker factors for age-related vascular diseases, since many genes within this family are associated with age-related diseases such as cardiovascular diseases,, atherosclerosis, type II diabetes, chronic kidney disease, neurodegeneration, cancer and age-related macular degeneration, in addition to the ageing process itself.

In this special issue of Current Molecular Pharmacology, several aspects of the biology of immunophilins have been addressed and with the purpose of providing an updated overview of the field. It is clear that we still have more questions than answers, a state of the art that keeps feeding our thoughts proposing new hypothesis or models and, above all, stimulating us to overcome the new rising challenges shown in the course of our careers. I hope that the high enthusiasm showed by all our contributors to make this endeavor possible will be appreciated by the readers. In this regard, wish to acknowledge the valuable viewpoint of all contributing authors and hope that this assemblage of perspectives will be a valuable resource for researchers in this and other related fields.

REFERENCES

[1] Heusler, K.; Pletscher, A. The controversial early history of cyclosporin. *Swiss Med. Wkly*, **2001**, *131*, 299-302.
[2] Ruegger, A.; Kuhn, M.; Lichti, H.; Loosli, H.R.; Huguenin, R.; Quiquerez, C. von Wartburg, A. Cyclosporin A, a Peptide Metabolite from Trichoderma polysporum (Link ex Pers.) Rifai, with a remarkable immunosuppressive activity. *Helv. Chim. Acta*, **1976**, *59*, 1075-1092.
[3] Wenger, R.M. Synthesis of cyclosporine. Total synthesis of "Cyclosporin A" and "Cyclosporin H". Two fungal metabolites isolated from the species Tolypocladium Inflatum GAMS. *Helv. Chim. Acta*, **1984**, *67*, 502-525.
[4] Borel, J.F. Comparative study of *in vitro* and *in vivo* drug effects on cell-mediated cytotoxicity. *Immunology*, **1976**, *31,* 631-641.
[5] Borel, J.F.; Feurer, C.; Gubler, H.U.; Stahelin, H. Biological effects of cyclosporin A: a new antilymphocytic agent. *Agents Actions,* ***1976***, *6*, 468-475.
[6] Tamura, K.; Kobayashi, M.; Hashimoto, K.; Kojima, K.; Nagase, K.; Iwasaki, K.; Kaizu, T.; Tanaka, H.; Niwa, M. A highly sensitive method to assay FK-506 levels in plasma. *Transplant Proc.,* **1987**, *19,* 23-29.
[7] Tanaka, H.; Kuroda, A.; Marusawa, H.; Hashimoto, M.; Hatanaka, H.; Kino, T.; Goto, T.; Okuhara, M. Physicochemical properties of FK-506, a novel immunosuppressant isolated from Streptomyces tsukubaensis. *Transplant Proc.,* **1987**, *19*, 11-16.
[8] Goto, T.; Kino, T.; Hatanaka, H.; Nishiyama, M.; Okuhara, M.; Kohsaka, M.; Aoki, H.; Imanaka, H. Discovery of FK-506, a novel immunosuppressant isolated from Streptomyces tsukubaensis, *Transplant Proc*., *19*, **1987**, 4-8.
[9] Sehgal, S.N.; Baker, H.; Vezina, C. Rapamycin (AY-22,989), a new antifungal antibiotic. II. Fermentation, isolation and characterization. *J. Antibiot. (Tokyo)*, **1975**, *28,* 727-732.
[10] Vezina, C.; Kudelski, A.; Sehgal, S.N. Rapamycin (AY-22,989), a new antifungal antibiotic. I. Taxonomy of the producing streptomycete and isolation of the active principle. *J. Antibiot. (Tokyo)*, **1975**, *28*, 721-726.
[11] Kluepfel, D.; Baker, H.A.; Piattoni, G.; Sehgal, S.N.; Sidorowicz, A.; Singh, K.; Vezina, C. Naphthyridinomycin, a new broad-spectrum antibiotic. *J. Antibiot. (Tokyo)*, *28,* **1975**, 497-502.

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