Professor Pierre MARQUET of University Hospital of Limoges

We interviewed Professor Pierre MARQUET, head of the Pharmacology, Toxicology and Pharmacovigilance department at the University Hospital of Limoges, France. His research area is pharmacology and toxicology. Since 2007, he has been the head of the INSERM research unit UMR 850 in "Pharmacology of immunosuppressive drugs in transplantation" (INSERM is the French National Institute of Medical and Health Research).
Professor MARQUET and Shimadzu started a collaborative project in 2013 that has already yielded several achievements.

Shimadzu:

Professor MARQUET, thank you very much for taking some time for this interview. First of all, could you tell us about the background of this collaborative research? Why did you choose Shimadzu?

Prof. MARQUET

The Laboratory of Pharmacology and Toxicology of the University Hospital of Limoges is one of the largest in France. It is divided into transplantation research activities (INSERM unit created in 2007) and clinical activities. In 2013, Shimadzu proposed to set up collaboration with a one-year loan of a triple quadrupole LCMS-8040. Due to the good results obtained, we decided to buy this year a triple quad LCMS-8050. The collaboration is currently ongoing with the loan of another LCMS-8050 system. This will help us meet our desires to develop new methods and work with two identical devices and to have a backup system.
Our most urgent development needs were in clinical and forensic toxicology. So, the LCMS-8050 was installed in this lab in order to develop techniques for drugs of abuse detection and determination. This collaboration helped us to take the plunge and use liquid chromatography-triple quadrupole mass spectrometry (LC-MS/MS) for the detection of illicit drugs, where we used to employ gas chromatography - mass spectrometry (GC-MS), which requires considerable sample preparation and analysis time. Other labs had already taken the step but we did not have enough LC-MS/MS instruments to dedicate one (or most of one of them) to illicit drug analyses.

Shimadzu:

Then could you outline your aims and let us know what methods have been developed so far?

Prof. MARQUET

In the early part of this collaboration, our aim was to establish four methods during the first year, but we have fallen behind. This can be explained both by a difficult start with the system configuration and the limited time we have been able to dedicate to such developments. Today, we have some pretty good results. Three of the four techniques we planned are currently being validated and the 4th is under development.
We have developed methods for the detection of drugs (cocaine and metabolites, opiates and opioids, amphetamines and analogs), a large number of anticonvulsants, and anticoagulants (including new oral anticoagulants). A method for cannabinoids is being optimized because we are facing a memory effect in the on-line extraction columns.
We had hoped to use online sample preparation systematically, as is already the case in our pharmacology lab. However, it is not working as well as we hoped, probably because we handle many heterogeneous molecules with different acid-base properties and/or polarities. Therefore, it has been difficult to find a single solid-phase extraction condition for all these molecules.

Shimadzu:

Why are you interested in such developments? What is your goal?

Prof. MARQUET

For most of these newly developed methods, the LCMS-8050 replaces more than one GC-MS. The latter requires long but also manual sample preparation. Budget restrictions being a strong reality in French hospitals, the lack of technicians is sorely felt. This technological switch allows us to maintain and develop our activity despite fewer technicians, while reporting the results faster. Another focus that we have in mind when doing new developments is the introduction of new illicit or therapeutic drugs to our panels of tests.

Shimadzu:

How are our instruments helping you?

Prof. MARQUET

When I think of Shimadzu instruments, sensitive and robust are the first two adjectives that come to my mind.
We use the QuEChERS preparation method, that is to say liquid extraction by salting effect. This preparation induces a dilution of the sample, when until recently we had to purify and then concentrate the samples prior to the analysis. Thus, the Shimadzu instrument's sensitivity saves much time, as it is not necessary to concentrate the samples any more. Also, dilution reduces matrix effects, which is a good thing.
Moreover, thanks to UHPLC and the system speed (run-time reduction), we have optimized our analysis times. Where in the past we needed 2 GC-MS systems, one LC-MS/MS system is now sufficient and there is time left for other analyses.

Shimadzu:

What are Shimadzu's strengths compared to other vendors?
(not limited to the instruments)

Prof. MARQUET

Apart from this specific collaboration, the "Pharmacology, Toxicology and Pharmacovigilance" department and Shimadzu are longtime collaborators. A strong relationship based on trust has been established and there are many reasons for this.
First of all, as I said earlier, the instruments are robust and sensitive, which is why there are so many Shimadzu HPLC and GC-MS systems in our department. In our laboratory, where many routine tests are carried out, it is important to have robust systems well maintained over time. Your good and reliable after-sale service distinguishes you from some of your competitors.
We are in a specific situation: we have a large analytical park but we cannot objectively renew it regularly. So we have to make it work as long as possible. Shimadzu is characterized by not planning system obsolescence and provides long-term support, which are very valuable assets.
Furthermore, our lab technicians can easily use the different instruments because of the common software for HPLC, GC-MS and LC-MS/MS.

Shimadzu:

Finally, could you please share any requests that you have with respect to instrument vendors?

Prof. MARQUET

The main suggestion I would make to scientific instrument vendors is not to neglect support and development assistance to customers. In a world where everyone is increasingly pressed for time, method implementation is a very important asset to stand out from other vendors.

Shimadzu:

It is important to know what you think of us and our collaboration. We will strive to meet your requests more than ever. Thank you very much.

Research Activities:

With the ultimate goal of treatment personalization in organ transplant recipients, the INSERM unit U850 pursues a translational research strategy to: (i) identify the pharmacokinetic, pharmacogenetic and pharmacodynamic factors influencing the response and tolerance to immunosuppressive drugs (ISD) and regimens; (ii) discover early, non-invasive biomarkers of graft lesions; (iii) and to set up treatment individualization tools, validate them clinically and transfer them to physicians. The unit also sets up cohort studies to measure the impact of treatment personalization on patient and graft survival, patients' quality of life and healthcare expenses.

Pierre MARQUET, Jean-Michel GAULLIER, Denis RAFFIER (from left to right)

Recent publications:

Pharmacokinetics

1. Woillard JB, Lebreton, Neely M, Turlure P, Girault S, Debord J, Marquet P, Saint-Marcoux F. Pharmacokinetic tools for the dose adjustment of cyclosporine in Hematopoietic Stem Cell transplant patients. *Br J Clin Pharmacol.* 2014 Oct;78(4):836-46.
2. Woillard JB, Bader-Meunier B, Salomon R, Ranchin B, Decramer S, Fischbach M, Berard E, Guigonis V, Harambat J, Dunand O, Tenenbaum J, Marquet P, Saint-Marcoux F. Pharmacokinetics of mycophenolate mofetil in children with lupus and clinical findings in favour of therapeutic drug monitoring. *Br J Clin Pharmacol.* 2014 Oct;78(4):867-76.

Pharmacogenetics

3. Woillard JB, Picard N, Thierry A, Touchard G, Marquet P; DOMINOS study group. Associations between polymorphisms in target, metabolism, or transport proteins of mycophenolate sodium and therapeutic or adverse effects in kidney transplant patients. *Pharmacogenet Genomics.* 2014 May;24(5):256-62.

Pharmacodynamics & PKPD

4. Carr L, Gagez AL, Essig M, Sauvage FL, Marquet P, Gastinel LN. Calcineurin activity assay measurement by liquid chromatography-tandem mass spectrometry in the multiple reaction monitoring mode. *Clin Chem.* 2014 Feb;60(2):353-60.
5. Noceti OM, Woillard JB, Boumediene A, Esperón P, Taupin JL, Gerona S, Valverde M, Touriño C, Marquet P. Tacrolimus Pharmacodynamics and Pharmacogenetics along the Calcineurin Pathway in Human Lymphocytes. *Clin Chem.* 2014 Oct;60(10):1336-45.
6. Daher-Abdi Z, Lavau-Denes S, Premaud A, Urien S, Sauvage FL, Martin J, Leobon S, Marquet P, Tubiana-Mathieu, Rousseau A. Pharmacokinetics and exposure/effect relationships of capecitabine in elderly patients with breast or colorectal cancer. *Cancer Chemother Pharmacol.* 2014 Jun;73(6):1285-93.
7. Daher Abdi Z, Prémaud A, Essig M, Alain S, Munteanu E, Garnier F, Le Meur Y, Marquet P, Rousseau A. Exposure to mycophenolic acid better predicts immunosuppressive efficacy than exposure to calcineurin inhibitors in renal transplant patients. *Clin Pharmacol Ther.* 2014 Oct;96(4):508-15.

Clinical trials & clinical cases

8. Gauthier T, Piver P, Pichon N, Bibes R, Guillaudeau A, Piccardo A, Pesteil F, Tricard J, Gardet E, Laskar M, Lalloué F, Marquet P, Aubard Y. Uterus retrieval process from brain dead donors. *Fertil Steril.* 2014 Aug;102(2):476-82.
9. Monchaud C, Marin B, Estenne M, Preux PM, Marquet P; the eDelphi-Lung Transplant Group. Consensus Conference on a Composite Endpoint for Clinical Trials on Immunosuppressive Drugs in Lung Transplantation. *Transplantation.* 2014 Jun 20. [Epub ahead of print]