

## An Interview with Dr. Marie-Pierre Dubé of the Montreal Heart Institute's Pharmacogenomics Center

In a recent landmark study by J.C. Tardif and colleagues<sup>1</sup>, Dr. Marie-Pierre Dubé and her team at the Beaulieu-Saucier Pharmacogenomics Center at the Montreal Heart Institute found that dalcetrapib — a Roche compound for raising a patient's high-density lipoproteins that failed to demonstrate efficacy in a large Phase III trial — may be efficacious for a subset of patients with a specific genetic background.

We spoke with Dr. Dubé about the study, which utilized a custom MassARRAY<sup>®</sup> assay to help validate genetic associations, and the future of her institution's pharma partnerships.

### Why did you focus on dalcetrapib?

MPD: Because it's interesting. There is a long history about whether it is a good idea to raise HDL cholesterol; no Phase III trials have proven the hypothesis yet. One compound, dalcetrapib, was efficacious in raising HDL cholesterol in its Phase III trial, but that did not translate into an overall decrease in cardiovascular events. We investigated to see if the clinical efficacy of that drug could be affected by genetics.

### What did you discover and what is dalcetrapib's future?

MPD: Our data indicates that a subgroup of patients actually do benefit from this drug. We found that for patients who are AA homozygotes at SNP rs197309 in the *ADCY9* gene, treatment with dalcetrapib could reduce cardiovascular events by 40% compared to those treated with placebo. What's more, those patients who did not have the AA genetic profile (GG patients) had a greater risk of cardiovascular events when treated with dalcetrapib. We also had good supporting evidence from the dal-PLAQUE-2 imaging study, in which we saw that patients



with the protective AA genotype had atherosclerosis regression and those with the GG genotype had atherosclerosis progression. The next logical step would be to conduct a Phase III randomized clinical trial to test dalcetrapib versus placebo in a genetically determined patient population. Such prospective clinical trial could provide a verdict on the HDL therapeutic approach and perhaps open the way to a new cardiovascular drug approach with a genetic companion diagnostic.

That last point is significant. Cardiovascular conditions can require patients to use some medications for several years. There is real value in gaining a better understanding of those drugs and how they can be used as efficiently as possible. While we have recently seen broad adoption of new drug development with companion diagnostics in oncology — for example Xalkori for treatment of small cell lung cancer in patients with tumors expressing an abnormal *ALK* gene — that is not the case for cardiology. This work can help open up a new era for genetics in the drug development pipeline for cardiovascular disease.

### How did you design that post-hoc dalcetrapib study to ensure genetic associations discovered were real?

MPD: Since there are very few post-hoc pharmacogenomics studies of Phase III trials done so far, there is no set model. It is up to statisticians to decide the most appropriate approach.

In our study, we tested for genetic associations with cardiovascular endpoints in the treatment arm. Any finding was then tested in the placebo arm to confirm that the association was specific to the treatment arm and we tested for interaction effects with the treatment arm using the full study population.

In terms of genetic testing, we took a brute force approach and tested over two million SNPs using an Illumina GWAS chip and then imputed millions more SNPs throughout the genome. As you know, we had a single genome-wide significant hit at *ADCY9*, which included some of the imputed SNPs. To confirm the findings were real signals, we designed a custom MassARRAY panel for a number of SNPs in the *ADCY9* gene, including our top imputed and genotyped SNPs and a few SNPs we were curious to analyze based on previous literature data. We re-genotyped everyone again from the dal-OUTCOMES trial and for the first time genotyped patients with DNA from the dal-PLAQUE 2 trial.

The advantage of the MassARRAY panel is that it is less costly than a GWAS chip and relatively fast to design internally. Plus, it provides a validation of the results we had obtained by using a different genotyping technology.

The number of patients included in both the dal-OUTCOMES and dal-PLAQUE-2 studies was the maximum number of samples available. Not every patient consented to donate DNA, so the study was done on a smaller but representative subset of the full study populations. But also, as the studies were mostly conducted on a white population, we had to exclude a few participants

who were not of Caucasian ancestry in our genetic analyses in order to prevent false positives or confounding signals. Unfortunately there weren't sufficient numbers of participants of different racial background to test the results in different population subgroups with sufficient confidence.

### Your group is involved in several other post-hoc pharmacogenomic studies. Why do you think drug developers are partnering with you?

MPD: Two factors. First, our lab runs at industry standard and complies with GLP. This can be very attractive for pharmaceutical companies as the full quality assurance system in place can easily be audited. But second, we are an academic institution and we have been proactive in developing post-hoc pharmacogenomic studies, doing the analysis, and getting the full academic value out of them — and also getting some of them funded via research grants. The Montreal Heart Institute also has an academic "CRO", the MHICC, which leads international trials. We have partnered with them to promote the value of parallel pharmacogenomic studies with their trials.

Many sponsors are looking to run smarter, safer trials earlier on in the drug development pipeline. In Phase I, for example, even a small fraction of poor metabolizers could be misleading. So, there is a real opportunity there. At our center, we're seeing a big shift in Phase I studies. More and more patients are being genetically tested for their metabolism profile, with recruitment contingent on the results.

### How will pharmacogenetic testing progress into wider clinical practice?

MPD: In an ideal world, preemptive testing would be universal, we would sequence someone's genome once early in life, put that information into a centralized database of medical records to be readily available to guide the selection of the most efficacious drug according to the patient's genetic profile. But in a

realistic world, discoveries are being made one at a time and the market opportunities are seized as they become available. This is leading more toward a system where patients get tested each time they need a drug with a specific companion diagnostic test.

### What will be the surviving model?

MPD: That's not yet clear. Pre-emptive sequencing isn't practical just now mainly because it's too costly.

But what is clear is that in the coming years we're going to see a lot more drug labels with genetic information. The Personalized Medicine Coalition just released a report stating that of all the novel new drugs approved by the FDA's Center for Drug Evaluation and Research in 2014, 20 percent had some recommendations for using a biomarker on the product monograph. This gives further evidence that the work we are doing here at the pharmacogenomics center can have a quick translation into clinical practice.

### How have clinical needs influenced your bioinformatics pipeline?

MPD: Pharmacogenetic results need to be expressed in terms that are meaningful to the practicing physician. That can sometimes be tricky and needs to be specific to each intended drug. For example, *CYP2D6* metabolizes a lot of drugs, and for some the poor metabolizer status is exposing patient to risk; for others it is the fast metabolizer status that is. So the test results may need to be adapted to the drug under consideration.

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### How has that influenced your use of the MassARRAY system?

MPD: When a pharmacogenomic test misses a few alleles of a metabolism gene, then we are no longer in a good position to infer whether a patient is a good or poor metabolizer. With GWAS chips, we often face this problem when there is only 80% of the important alleles in a gene, and 20% are missing to make a reliable phenotype call. Sequencing can also be unreliable for some genes such as *CYP2D6*, unless in the hands of a skilled scientist. Due to that, we usually run Agena Bioscience's iPLEX® Pro ADME PGx panel in parallel to a GWAS chip for our pharmacogenomic studies. The panel covers the majority of essential alleles needed to make reliable phenotype calls. We infer phenotypes straight from the iPLEX panel and we have developed a validated pipeline to do so. This has been a very useful panel for us.

<sup>1</sup>Tardif, JC., et al. Pharmacogenomic Determinants of the Cardiovascular Effects of Dalcetrapib. *Circ Cardiovasc Genet.* 2015 Jan

