Interview

An interview with *Pharmacogenomics* for the breast cancer special focus issue

Richard Weinshilboum speaks to Natalie Harrison, Commissioning Editor

Richard Weinshilboum is the Mary Lou and John H Dasburg Professor for Cancer Genomics Research, Chair of the Division of Clinical Pharmacology, and a Professor of Molecular Pharmacology and Experimental Therapeutics and Medicine at the Mayo Clinic, Rochester (MN, USA). He received his BA in Chemistry and Zoology from the University of Kansas (KS, USA) and an Exchange Fellowship from Tuebingen University (Germany) before gaining his MD from the University of Kansas Medical School (KS, USA). He completed his residency in internal medicine at the Massachusetts General Hospital (MA, USA). Weinshilboum is Co-Principal Investigator of the Pharmacogenetics of Phase II Drug Metabolizing Enzymes research group, one of the 14 scientific research projects comprising the NIH Pharmacogenomics Research Network, a nationwide collaboration of scientists involved in the discovery and translation of genomics in order to enable safer and more effective drug therapies. The Mayo Clinic NIH Pharmacogenomics Research Network Center studies the pharmacogenomics of drugs that are used to treat cancer – especially breast cancer and leukemia – as well as neuropsychiatric diseases. These studies apply state-of-the-art genome-wide techniques and next-generation DNA sequencing to discover novel genomic variants that influence response to the therapy. This is always followed by functional and mechanistic pursuit of the genes identified. Another major component of Phase II Drug Metabolizing Enzymes activities involves the systematic ‘translation’ of this pharmacogenomic information to the bedside.

Richard M Weinshilboum

Mayo Foundation Rochester, Division of Clinical Pharmacology, 200 First Street, SW Rochester, MN 55905, USA
weinshilboum.richard@mayo.edu

■ Following your residency in internal medicine, what sparked your research interest in pharmacogenomics?

After finishing my medicine residency at the Massachusetts General Hospital (MGH; MA, USA), one of the Harvard (MA, USA) teaching hospitals, I was fortunate to be accepted into the NIH laboratory of Dr Julius Axelrod. Julie was a gifted and creative scientist as well as an inspiring mentor – in fact, I was working in his laboratory when he received the Nobel Prize in 1970; I bought his champagne that morning! It became very clear to me during that experience that I wanted to pursue research in pharmacology, which had been my interest since medical school at the University of Kansas (KS, USA).

After completing residency training at the MGH, my options were to return to the NIH or to go to an academic medical center; the Mayo Clinic (MN, USA) was just opening its medical school in 1972, and I went to Mayo predominantly to pursue research, but also to participate in the creation of a medical

school within a pharmacology department. When I arrived, I pursued genetic research, which was very unusual for a translational pharmacologist at a time that my students and fellows now refer to as the ‘Paleolithic Era’. What that immediately led to was the study of genetic variation in enzymes; more specifically, Phase II drug-metabolizing enzymes, which not only metabolize drugs but also neurotransmitters and hormones, including the estrogens.

As a result, by the end of my first decade at Mayo, we had discovered the *TPMT* genetic polymorphisms, and soon after, their association with serious adverse reactions to the use of thiopurines to treat childhood leukemia; this is now one of the striking examples of genetic polymorphisms that have undisputed clinical utility.

■ When was the NIH Pharmacogenomics Research Network established & what was its initial focus?

In the late 1990s, I received a telephone call from Dr Rochelle Long, a project

officer at the NIH's National Institute of General Medical Sciences (NIGMS; which supported all of my grants from the 1970s). She basically said, "Well, we've been funding you for years to study pharmacogenetics, let's talk about that." I thought it was strange that she would call after 20 years of supporting our research and say "let's talk about it"; however, we talked for half an hour and I subsequently thought nothing more about it. Several months later she called back and said that the NIGMS was trying to establish where it could make a useful contribution in the post-genome-project world (because in the late 1990s it was clear that the genome project was going to be finished successfully) and they wondered whether it might be – in part – in pharmacogenetics.

She asked if I would be willing to chair a taskforce, composed one-third of representatives from the traditional genetics community, one-third from the pharmacogenetics community (which was based in the clinical pharmacology disciplines), and one-third from industry. I agreed to chair the taskforce, with Dr Long as the NIH administrator responsible, and we made a report to the Advisory Council for NIGMS in 1999 recommending that they create a network focused on pharmacogenetics.

The council approved our report and the Pharmacogenomics Research Network (PGRN) was established (originally the NIH Pharmacogenetics Research Network). This network was predominantly funded by the NIGMS, but Dr Long engaged several other NIH institutes, such as the Heart, Lung and Blood Institute (NHLBI) and the National Cancer Institute (NCI) to support a reasonable portion of the expense. The current PGRN now has 14 centers and several of those centers have cancer as part of their portfolio. Our center at the Mayo Clinic has focused on the pharmacogenomics of breast cancer and on psychiatric illness – specifically, depression. I think that there is a great deal going on in the pharmacogenomics of breast cancer research right now, and it also provides an exciting example of international collaboration and how the way in which we organize and fund science can catalyze novel scientific advances.

■ Over the past decade, this research program has expanded & now places an emphasis on discovering novel genomic variants that influence response to breast cancer therapy; what, in your opinion, have been the Mayo PGRN's major achievements in this field to date?

Our initial focus has been on the 'endocrine' therapy of breast cancer in collaboration with the Mayo Clinic NCI Specialized Program of Research Excellence in breast cancer, with my colleague Dr James Ingle as Principal Investigator. Dr Ingle has been involved in breast cancer endocrine therapy – selective estrogen receptor modulator or aromatase inhibitor therapy – for decades and is also deeply involved in large, randomized trials of these classes of drugs. Those collaborations make it possible to apply genome-wide techniques to identify 'SNP signals' and then to functionally validate those signals and pursue the underlying mechanism(s). What we have done is to not merely use genome-wide association studies (GWAS) to identify signals to obtain a biomarker, but my talented Co-Principal Investigator for the Mayo PGRN, Dr Liewei Wang, has created a genomic data-rich cell line-based model system that has enabled us to pursue GWAS signals, first to functionally validate them and then, to understand underlying mechanisms.

A good example is a study that the Mayo PGRN published in the *Journal of Clinical Oncology* in November 2010 in which we used samples from a very large aromatase inhibitor study, the MA.27 study from the NCI of Canada Clinical Trials Group. This study involved 7576 women, of whom 72% donated DNA. The major cause for these women dropping out of that study was severe musculoskeletal pain as a side effect of aromatase inhibitor therapy. We performed a case-control GWAS in which we took patients with grade 3 or 4 musculoskeletal pain or any woman who stopped taking the aromatase inhibitors because of musculoskeletal pain. We had two matched controls for each of these 'cases' and identified a GWAS signal in the *TCL* gene cluster on chromosome 14.

We then used the cell line model system that Dr Wang developed to show that the SNP with the lowest p-value created an

estrogen response element, which resulted in increased expression of the *TCLIA* gene in response to estrogen exposure and that the *TCLIA* gene, in turn, regulated the transcription of a series of cytokine and cytokine receptor genes, thus linking the SNPs with what the drug did, showing that estrogens would induce *TCLIA*, and linking that gene to the clinical phenotype by virtue of its regulation of cytokine and cytokine receptor expression.

■ **The Mayo Clinic NIH PGRN Center was established in 2000; what model systems & techniques have made this center's work possible?**

I have already mentioned the cell line-based model system developed and applied by Dr Wang and the application of GWAS technology – neither of which existed in 2000. The PGRN also has a network-wide 'deep sequencing' resource based in the NHGRI-funded genome centers at Baylor College of Medicine (TX, USA) and Washington University St Louis (MO, USA), as well as an NHLBI funded center at the University of Washington. This network resource is available to any of the 14 centers and arose as it became clear that we needed to move to next-generation DNA sequencing. We have several ongoing projects utilizing this network resource. For example, if we find a signal during a GWAS, we will then take those samples and perform deep sequencing across the signals to search for rare variants that might also explain some of the effects of these areas of the genome on breast cancer risk and/or drug response phenotypes – either adverse drug reactions or genetic variation in drug efficacy.

In pharmacogenomics we will continue to apply genome-wide techniques, such as GWAS, but as soon as the cost comes down, we will also increasingly apply next-generation sequencing.

■ **What efforts are in place at the Mayo Clinic to translate this new pharmacogenomic information to the bedside?**

The PGRN has functioned both as a 'discovery engine,' as I just described, but also as a catalyst to help overcome institutional and other barriers to bringing this aspect of genomic science to the bedside. Francis Collins, Director for the NIH, has said

publicly, and I certainly agree, that one of the very first examples of the clinical application of genomics will be pharmacogenomics.

The PGRN has played a leadership role in terms of clinical implementation in a variety of ways, as well as by catalyzing the whole field by providing access for academic investigators to the technology required to make novel discoveries by applying genome-wide techniques. I would predict that this will be true of breast cancer, as well as many other medical disciplines. I think the day is rapidly approaching when patients will arrive with their entire genome on a flash drive or some equivalent device or stored somewhere in the 'cloud'. To take advantage of those developments and apply them to breast cancer is going to be fascinating.

At the discovery end of the spectrum, there is a great deal we do not understand about drug response, even about drugs with which we have a great deal of experience – drugs like the aromatase inhibitors and selective estrogen receptor modulators. For example, at the Mayo Clinic we are initiating a very large neoadjuvant trial, in which we will sequence both the tumor and germline genomes, perform RNA-sequencing of the tumor, and use neoadjuvant therapy to determine response of the tumor. Then, after we identify genomic signatures, we hope to separate patients with different pathological responses in the neoadjuvant setting and use 'individualized' targeted therapies to treat these women (we have not done this yet). We are trying to use breast cancer as one of the major entrees to the application of adaptive, genome sequence-guided cancer therapy.

■ **In your talk on the pharmacogenomics of breast cancer endocrine therapy at the last Pharmacogenomics and Personalised Medicine 2011 conference (Cambridge, UK, September 2011), you stressed that we now need to move beyond biomarkers to functional validation, mechanistic insight & novel targets. How close do you think we are to being at that next level?**

Earlier I quoted the paper that we published in the *Journal of Clinical Oncology*, which focused on the side effects of aromatase inhibitors; however, in the large P-1

and P-2 National Surgical Adjuvant Breast and Bowel Project breast cancer prevention trials we also managed to gain novel mechanistic insights by pursuing the function of signals that came from GWAS. These studies involved 33,000 women and formed the basis for the US FDA's approval of both tamoxifen and raloxifen for the prevention of breast cancer in high-risk women. We also have a third study, in which we have taken a very similar approach and, mainly because of availability of the cell line model system that Dr Wang has developed (for which we have genome-wide SNPs, genome-wide expression and genome-wide CpG methylation in three different ethnic groups); we have the ability to pursue many signals to a mechanistic level. I think that we all have a responsibility to move beyond biomarkers to function and mechanisms, and now have examples which demonstrate that this is possible.

■ In your opinion, what are the biggest challenges facing pharmacogenetic researchers today?

First of all, the issue of replication when using genome-wide techniques is a very significant challenge in pharmacogenomics because you cannot just repeat a clinical trial to replicate a p-value that may be near or just below genome-wide significance. One of our greatest challenges is to find ways to gain access to sample sets that might be available and to bring the breast cancer clinical trial community together in order to collaborate and learn what we can do to benefit patients with this disease. I also think that one of the biggest challenges facing pharmacogenomic research is the cost of the technologies required to do this type of research in a 2012 setting – which involves very large studies and creating groups of investigators who bring complementary expertise to the table. This is not something that can be done in the way that I started my career, in what I refer to as the 'Mom and Pop store' era – one investigator and one technician in one laboratory. That is not to criticize that approach since, ultimately, all of science depends on some bright, usually young, person with a creative, unconventional idea. We need to create structures that will allow those bright young people to exercise their creativity in

the setting of the very expensive technology that is available today.

At this very difficult economic time, a time when the opportunities to apply biomedical science to gain insight into the underlying biology responsible for drug response, and differences in drug response to therapy have never been greater, I think the greatest challenge is keeping these young people engaged, because no matter where we happen to live, whether it is Germany, Japan, the UK or the USA, they represent our future. I do worry that our social, political and economic leaders may not understand that as well as those of us who have the privilege of working with these talented young investigators every day.

■ How do you see the field of breast cancer pharmacogenomics progressing in the next 10 years?

I think that we will look at each individual tumor in an individual fashion, have tailored therapy and have methods that will allow us to predict response to therapy. Will that be in 10 years? I don't know, but that is clearly where cancer in general, and breast cancer in particular, are moving. I believe that now is the most exciting time that has ever existed to be involved in studies of the pharmacogenomics of breast cancer.

Acknowledgements

The author would like to give credit to the National Institute of General Medical Sciences and R Long, who has been a gifted leader and energetic advocate for pharmacogenomics, to Y Nakamura and his colleagues at the RIKEN Center for Genomic Medicine for their vision in collaborating with the Pharmacogenomics Research Network and for our colleagues in Germany, in particular P Fasching, who has been a leader in helping to bring the Pharmacogenomics Research Network together with German breast cancer research.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.