Interview

Dr Ronald Krauss speaks to Shreeya Nanda, Commissioning Editor

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Ronald M Krauss, MD, is Director of Atherosclerosis Research at Children's Hospital Oakland Research Institute (CA, USA), Guest Senior Scientist in the Life Sciences Division of Lawrence Berkeley National Laboratory (CA, USA), and Adjunct Professor in the Department of Nutritional Sciences at the University of California at Berkeley (CA, USA). He received his undergraduate and medical degrees from Harvard University (MA, USA) with honors and served his internship and residency on the Harvard Medical Service of Boston City Hospital (MA, USA). He then joined the staff of the National Heart, Lung, and Blood Institute in Bethesda (MD, USA), first as Clinical Associate and then as Senior Investigator in the Molecular Disease Branch. Dr Krauss is a member of the American Society for Clinical Investigation, the American Federation for Clinical Research, and the American Society of Clinical Nutrition. He has received a number of awards including the American Heart Association Scientific Councils Distinguished Achievement Award. Dr Krauss has been a Senior Advisor to the National Cholesterol Education Program and the American Heart Association Council on Nutrition, Physical Activity and Metabolism. Dr Krauss has published more than 300 research articles and reviews on genetic, dietary and drug effects on plasma lipoproteins and coronary disease risk.

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You have a degree in medicine from Harvard University: what led to your interest in the genetics of lipoproteins and coronary artery disease risk?

I became interested in determining the causes of heart disease early on, from childhood, because my father had heart disease at a young age and I grew up with a desire to understand and cure this condition. When I reached my training, I discovered the work of a group at the NIH that had started to decipher some of the genetic contributions to heart disease and their effects on cholesterol, and at that point I decided that that was what I was going to focus on.

What factors play a role in interindividual variations in the response to cholesterol-lowering drugs?

This is turning out to be a very complex picture because of the many systems that are involved in regulating cholesterol and lipoprotein metabolism that have genetic influences. The drugs that we use, statins in particular (which is what my focus has

been in recent years), operate in known ways to modify cholesterol metabolism, but the response is influenced by many systems that we are just beginning to understand. Genetics is only a part of the story; we know that other factors, such as age, ethnic and racial differences among individuals, which may involve genetics, play a role, and there are probably other factors, such as diet, that also come into the picture.

You have recently published a study showing that alternate splicing of *HMGCR* could explain the differences in the response to treatment with statins – could you explain this work?

We were led to study this gene, *HMGCR*, because it codes for the enzyme HMG-CoA reductase, which is a critical determinant of blood cholesterol synthesis and low-density lipoprotein (LDL) cholesterol levels in the blood; in particular, it is the target for statin inhibition, and this is the mechanism by which statins reduce cholesterol production. In studying this gene, we, and others, had determined that

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there were certain genetic variants that appeared to be associated with differing response to statins in terms of the magnitude of LDL cholesterol reduction. Once we found those variants, we wanted to try to understand the mechanisms by which the genetic variation led to a reduced response to statins, and we turned our attention to a recently described process by which the *HMGCR* gene is modified in the course of its transcription. When a gene is transcribed, there is splicing or clipping out of the sequences between the coding regions, and sometimes you can have alternative restitching of the remaining portions of the gene. In the case of *HMGCR*, we studied one such form that we determined was relatively insensitive to statin inhibition, and part of the genetic effect that we discovered was due to the fact that the genetic variation promoted an increase in the amount of the alternatively spliced enzyme. Then, when we looked at our entire population of statin-treated subjects, we found that there was splicing to varying degrees in all individuals, so there are other factors besides the specific genetic variants that influence splicing. However, overall, if an individual had a greater degree of splicing, and this was studied in cells from these individuals, they turned out to be less responsive to statins, whereas individuals with relatively low levels of splicing were more responsive. This accounted for nearly 10% of the variability in the LDL response to statins, which is a pretty significant effect, but by no means does it account for the full range of variation that we see among individuals.

You are principal investigator of the 'Pharmacogenomics and Risk of Cardiovascular Disease' project of the PharmGKB – can you tell me about it?

The NIH has a group of investigators who have grants as part of the Pharmacogenetics Research Network. My component of that, the Pharmacogenomics and Risk of Cardiovascular Disease (PARC) grant, is one that is focused on identifying genetic modifiers

of response to drugs that are used to reduce the risk of cardiovascular disease. The main focus of our current program is to better understand genetic effects on statin response, both in terms of benefits of statins and some of the adverse effects that can occur involving muscle tissue. Although the latter are relatively uncommon, they can be a clinical problem for patients, and in some cases can actually be very severe. With that mission, we have systematically examined genetic variation in genes that are considered to be involved in these processes.

More recently, with the availability of genomic technology, we, as well as other groups, have utilized genome-wide screening for genetic variation in an attempt to provide a more comprehensive picture of the overall genetic contribution to statin response. This is a very ambitious effort, testing for hundreds of thousands of genetic variants in thousands of individuals. Sifting through the results using sophisticated statistical techniques is a challenge, and it is currently where our efforts are being focused: to determine not just where there might be associations, but also where we can confirm in other populations that these associations are valid. We need to replicate them because there is always a possibility for a false finding when one is carrying out that many statistical tests, and we are now assembling a number of studies that we will use to help confirm our findings.

Finally, of greatest interest, at least in my laboratory, is the proof that the variations that we come up with have effects that we can demonstrate by functional studies, such as the one I described for the *HMGCR* gene. It is very important to be able to draw conclusions about the genetic association findings by understanding the underlying mechanisms. In addition, this provides information that could be of value in understanding fundamental processes affecting cholesterol metabolism and heart disease risk, and could perhaps even lead to new drug targets that modify the pathways that are influenced by these genetic variants.

What other projects are you involved in?

A large part of my program is focused on nutrition and its effects on lipoprotein metabolism and heart disease risk, and some of the same issues come up with diet as in the case of statins and other drugs. In both cases, we are trying to understand the pathways that may influence the magnitude of the type of response that we see. We are finding individuals who actually show adverse effects on their lipid profile in their response to low-fat diets that are considered to be therapeutic, while others show beneficial effects. As in the case of pharmacogenetics, we have an interest in identifying the genetic differences among individuals that may make them more susceptible to these diet responses. This is an area that is called nutrigenomics, and between nutrigenomics and pharmacogenomics we have tried to cover a spectrum of treatment opportunities that can be used for helping to manage risk for cardiovascular disease.

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When do you see the clinical translation of pharmacogenomics becoming a reality and what, in your opinion, are the main hurdles?

Pharmacogenetics/pharmacogenomics has been around for a while and there actually have been some accomplishments that have reached the clinic, primarily in the area of genes that affect drug metabolism. In fact, there are some genetic tests that are currently being offered that help to identify people who may be susceptible to adverse reactions to certain drugs that are used in cancer treatment. Thus, that aspect of pharmacogenetics is already working its way into clinical practice.

The type of work that my group is involved with is disease genetics and how drug response may be influenced by genetics in ways that could affect the disease process. That is a more challenging effort because heart disease, even cholesterol metabolism, like many other conditions that we struggle with in clinical medicine, such as obesity and diabetes, are complex genetic traits with

many interactions between genes and environmental factors that require very extensive statistical analysis, as well as large amounts of data. Right now, we are fortunate that we have tools that allow us to take on this type of analysis, but this type of pharmacogenetics is far from being ready for clinical application. Within 5 or 10 years we should learn more about how this information might be used, and it may be that it will be used in a way that we have not yet anticipated. For example, the initial thinking in pharmacogenomics was that we might have a panel of genetic markers that individuals could use to help sort out their disease risk and which drugs might be most appropriate for them. That is still the goal, and it is still very much within the realm of possibility, but it may turn out that we will use genetics in a more selective way; for example, in families where there is a particular form of heart disease we may then take individuals from those families and do genetic tests to determine which form of the syndrome or disease they have and which pathways are involved. In this way we can apply genetics selectively to help refine the clinical characterization of patients, and that could lead to more rational decisions as to which drugs will be most appropriate. Thus, rather than using these tests to screen a population as a whole, I think it is more likely that we will use them to help refine the diagnoses of individuals who are being considered for treatment.

Where do you think your efforts will be focused in the next 5 or 10 years?

We are probably going to wrap up the strictly genetic phase of our work in the next few years, and I see the next stage of research, certainly from the standpoint of my own interests, as trying to understand how the genes that

we have identified function. This will require the integration of genetic knowledge with biochemistry, physiology and clinical medicine. This is what is called systems biology, in current terminology. I am very excited about the prospect of being able to take our genetic findings and apply them in clinical experiments that will allow us to work out the mechanisms and pathways by which these genetic variants are operating.

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