Veronique interviewed Professor Stephen Rappaport about the exposome concept and the importance of elucidating exposures that cause chronic diseases. A shorter version of this interview can be read in the first issue of the EXPOsOMICS project Newsletter.

Stephen Rappaport is a pioneer in the emerging field of 'Exposure Biology' and a strong proponent of the concept of the 'Exposome' as a new paradigm for environmental health. Prof Rappaport is Director of the Berkeley Center for Exposure Biology at the University of California, Berkeley. Much of his current research involves the development and application of blood protein adducts as biomarkers of exposure to toxic chemicals arising from inhalation, ingestion, and endogenous processes. For the EXPOsOMICS project he is working on the adductomics work package, WP6 together with David Phillips from Kings' College, London.

How do you define the concept of exposome and how does it complement the genome?

We think of the exposome as the totality of exposures that might contribute to disease. Since it is widely accepted that diseases are caused by the combined effects of genetic factors and exposures, the exposome is a natural complement to the genome in epidemiologic research. By comparing both exposomes and genomes between diseased and healthy people it is possible to find those exposures and genes (or their combination) that are causal factors.

It is also important to point out that the exposome includes all exposures, not just exposures to air and water pollution. Because most people equate the term 'environment' with 'pollution', I prefer the term 'exposome' when considering non-genetic factors. This is not to say that pollution is not important or that pollutants do not contribute to diseases. For example, studies conducted by the WHO indicate that exposure to particulate matter from air pollution and indoor smoke accounts for roughly 13% of all deaths in the world, while cigarette smoking and lead pollution account for another 12% and 1% of worldwide mortality, respectively. But aside from these examples, no other pollutant or class of pollutants appears to cause as much as 1% of global mortality. Diet and exercise, on the other hand, cause about 25% of global deaths. When we metabolize our food, we convert large molecules - carbohydrates, fats and proteins – into small molecules – sugars, fatty acids, nucleic acids and amino acids – that are essential for life. Much of this metabolism takes place in our intestines, where bacteria (the microbiota) convert dietary constituents into chemical products that re-enter the blood. Some of the chemicals produced by the microbiota appear to be beneficial to our health while others are not.

Could you give some examples of effects of the microbiota?

Although research into the health effects of the microbiota is relatively new, some interesting disease associations are emerging. For example, studies have shown that babies delivered by caesarean have different populations of microbiota than babies delivered vaginally. During a normal vaginal delivery, the baby is inoculated with the faecal and vaginal bacteria from the mother. This appears to be a desirable outcome since it leads to 'healthy' infant microbiota that promotes development of a good immune system. But following a caesarean delivery the baby is inoculated with bacteria from the mother's skin, and these microbiota are apparently not well suited for establishing the immune system. Thus, caesarean babies appear to have greater risks of infections by pathogens in early life and for

developing childhood asthma. Other studies have shown that metabolism of common nutrients by some microbiota produce undesirable chemicals, like trimethylamine, that appear to be associated with chronic diseases.

Why is it important of elucidate the constituents of the exposome that cause diseases?

Although, most people think that the genome is the major cause of these chronic diseases - cancer, cardiovascular disease and respiratory disease - this is a misconception. In fact, the accumulated evidence shows that the genes have a relatively small influence on the incidence of chronic diseases. For cancer, the attributable risk associated with genetic factors is typically less than 2%, although it can be higher for particular tumours, e.g. 10% - 20% for breast and prostate cancers. Likewise the attributable genetic risk for coronary heart disease is rather modest, probably less than 15%. So if we want to find out what accounts for 85% - 90% of chronic-disease risks, we need to move away from the genome and investigate the non-genetic causes, that is, the exposome. This is why Chris Wild originally proposed the idea of the exposome in 2005.

How can you characterize all exposures that might cause diseases?

This can be done using samples of blood from disease cases and controls, preferably from cohort studies like the European Prospective Investigation into Cancer (EPIC). Although it has become rather routine to characterize virtually all genes in such samples using genome-wide-association studies (GWAS), relatively little attention has been paid to parallel evaluations of the exposures, i.e. exposome-wide-association studies (EWAS). A promising approach for performing EWAS involves measuring all small molecules in blood – some people refer to this as untargeted metabolomics - and it is now possible to detect more than 30,000 small molecules in a single blood specimen. This collection of small molecules includes contributions from all external and internal sources – food, endogenous processes, microbiota, drugs, pollution and lifestyle factors – and thus gives us a rather complete view of exposure. Other classes of chemicals, including metals, proteins and foreign DNA and RNA, can also be investigated in a complementary fashion.

What exposures will your project (adductomics) investigate?

The project that David Phillips and I are coordinating (WP6) is investigating a particular class of molecules called reactive electrophiles that result from metabolism of foods and pollutants, oxidation of lipids and other endogenous processes. Although reactive electrophiles are intrinsically toxic, they cannot be measured directly in blood because they react with other molecules very rapidly. In fact, the reactions between electrophiles and important biomolecules, like DNA and proteins, are the initiators of cancers and other disease processes. So to get information about the levels of reactive electrophiles in human populations, we are measuring products of their reactions with human serum albumin, which is major blood protein. These reaction products are termed ‘adducts’ (chemical shorthand for ‘addition products’) and - because we are looking at the totality of adducts at a particular reaction site in the albumin molecule - we refer to the methodology as ‘adductomics’. We will use adductomics to investigate exposures to reactive electrophiles arising from both pollution and dietary sources using blood obtained by other work packages in the Exposomics programme.

How important is the concept of the 'Exposome' for you and what impact do you expect to see?

I think that the exposome could be the key to our understanding the causes of complex chronic diseases that have baffled health scientists and physicians for the last hundred years. As mentioned at the outset, diseases are caused by combinations of genes and exposures, with exposures being more important. Although we can use GWAS to comprehensively evaluate genetic factors, complementary studies of exposures have been lacking. Now we can use the umbrella of the exposome to develop and apply new methods to characterize all bioactive chemicals in the body and – through EWAS - to pinpoint those that cause disease. I trust that the Exposomics programme will find some of these chemicals, whether they originate from the diet, microbiota, pollution or other sources. Once we discover these discriminating exposures, we can help people live longer and healthier lives. That would be very cool.

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For further information about the EXPOsOMICS project please visit www.exposomicsproject.eu.

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