Interview

Perspective on the application of pharmacogenomics in the treatment of cancer

Professor Roland Wolf (FRSE, FMedSci, FRSA) is the co-director of the Dundee Biomedical Research Institute (Dundee, Scotland, UK) and Honorary Director of the Cancer Research UK Molecular Pharmacology Unit (Dundee, Scotland, UK). His research interests are understanding the pathways that determine the sensitivity of cells to drugs, environmental agents and chemical toxins, particularly molecular and genetic studies on how chemical agents interact with cells, how this influences their therapeutic and toxicological properties and how genetic polymorphisms in the genes involved relate to disease susceptibility, adverse pharmacology and toxicology. Specific current projects focus on preclinical drug development, pharmacogenetics, cancer therapy and chemoprevention. Professor Wolf has published approximately 450 scientific papers in peer reviewed journals. He is a member of many national and international boards and advisory groups and is currently a member of the Scottish Scientific Advisory Council. In 2001, he co-founded a company, CXR Biosciences (Dundee, Scotland, UK), currently comprising of 42 staff. In addition to providing drug discovery and development services, the company has a major focus developing new models for to accelerate the drug development process and reduce attrition when drugs enter man. Professor Wolf has been the recipient of a number of awards including the Gerhard Zbinden award in toxicology, The ISSX European Scientific Achievement award and the Scottish Enterprise award for the individual contributing most to the development of life sciences in Scotland.

Roland Wolf

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■ You are currently an Honorary Director of Cancer Research UK. How did you become involved with this charity?

I am currently Honorary Director of the Cancer Research UK Molecular Pharmacology Unit and Director of the Biomedical Research Institute based in Dundee. The Biomedical Research Institute comprises 150 staff, containing 19 research groups working on a variety of subjects relating to basic translational and applied medical science. We have particular interests in diabetes and cancer. I became involved with Cancer Research UK over 25 years ago, when I took up the position of Director of the laboratories in the then Imperial Cancer Research Fund Molecular Pharmacology Unit. In those days we had a particular interest in defining novel pathways of anticancer drug resistance and in anticancer drug pharmacology.

■ Could you briefly discuss some of your research projects linked to Cancer Research UK?

My research has always involved studies into the understanding of how chemicals interact with cells, which is of key importance in the etiology of human disease, in chemoprevention and in the development and use of drugs. My work has included a wide range of approaches involving biochemical, pharmacological and genetic studies, both in humans and in laboratory-based models. Our current research program has a number of specific interests, particularly in delineating the functions of mammalian drug metabolism and detoxification enzymes. These studies include work on the cytochrome P450-dependent monooxygenase system, detoxification and disease etiology mediated by glutathione S-transferases, and studies into the role of the Nrf2 antioxidant signaling cascade in disease susceptibility and anticancer drug resistance. We also currently have major programs in translational research, particularly on developing new paradigms for the personalized treatment of cancer patients.

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■ What are the main objectives that you hope to achieve with your research?

The main objectives of our research are to develop an in-depth understanding of the pathways that define cellular responses to chemicals as they relate to disease etiology, prevention and drug response. We have a particular interest in defining genetic and phenotypic variation, which relates to adverse drug reactions or drug efficacy.

■ Pharmacogenomics is a main focus of your research. What specifically led to your interest in this area?

One of the major drivers in the concept of personalized medicine has been our dramatic increase in understanding of drug metabolism. This has always been a cornerstone of my research work and a logical continuation from my postdoctoral studies in the USA. Moving to the UK in the early 1980s, and the obvious need for personalized medicine in cancer patients, together with the fact that genetic tools were now available to allow us to identify the molecular basis of inherited polymorphisms, provided the basis for my engagement in this research area. In the 1980s, this led to extensive studies on the cloning and characterization of mammalian and human cytochrome P450s and glutathione S-transferases and, at the beginning of 1990, the identification of the major gene defect resulting in the cytochrome P450 *CYP2D6* gene.

■ Adverse drug reactions and resistance to chemotherapy is a growing problem with many of the anticancer drugs that are available. How do you think that these problems could eventually be eradicated?

There are exceptional opportunities emerging for developing new treatments for cancer. I am convinced that the treatments will be nowhere near as toxic as currently applied therapies. It remains to be seen what adverse drug reactions may emerge from using these new therapeutic approaches. However, our understanding of genetic selection and the genetic changes that cause tumors to

form will inevitably mean that therapies will become more targeted to particular tumor genotypes and phenotypes. This will lead to the characterization of individual tumors and the identification of the most appropriate therapeutic intervention. This will inevitably involve both a detailed understanding of the patient's phenotype and genotype as well as the tumor phenotype and genotype.

■ What do you think is now needed to further enhance anticancer therapies?

Some of this is already discussed above. In order to fully understand and treat cancer successfully, there is an urgent need to have coordinated global research initiatives to fully characterize the molecular and genetic changes in different tumor types, as well as a much more detailed analysis of the phenotypic factors such as stromal interactions which drive tumor progression. In addition, far too little emphasis in anticancer drug development is given to clearly identify that a particular drug target will be efficacious and too little consideration is given to the optimization, pharmacodynamic and toxicokinetic parameters that define patient response and drug side effects. Although good patient responses can be achieved by using currently available anticancer drugs, there is a serious shortage of new agents demonstrating efficacy in the clinic. Thus, in order to improve cancer therapy we need to better understand the parameters that define drug response as well as to develop new agents that work.

■ How far do you think we are to achieving individualized chemotherapy routines for the most common cancers in clinical practice? The treatment of cancer has probably been one of the first research areas where personalized medicine was applied, for example, in the use of tamoxifen (AstraZeneca, UK) and similar drugs in the treatment of estrogen receptor positive cancer. There is also a considerable amount of emerging data indicating that mutations in particular pathways, for example, in the Ras signaling cascade, can be a major determinant in antitumor drug response. Over the next 5–10 years,

I am convinced that the way in which anticancer drugs will be applied will become much more sophisticated and targeted to the individual patient. The instigation, however, of such new experimental approaches into clinical practice is not trivial.

■ In what direction would you like to see your research heading in the future?

My research work will continue on the molecular and genetic factors that define drug responses, with increasing emphasis, however, on identifying novel approaches

for cancer therapy with the need for personalized medicine.

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