PHARMACOGENETICS OFFERS HOPE

Professor Michael Pepper of the Wits School of Anatomical Sciences.

A recently returned award-winning medical scientist is stirring major excitement in South Africa with a pharmacogenetic approach to drug therapy in general, and to AIDS in particular. The latter has the potential to radically reduce drug-resistant strains of the HIV virus through viral genome sequencing.

Some development of drug-resistant strains in the HIV-positive population is considered inevitable in spite of the best managed antiretroviral roll-out systems because of South Africa's demographics, infrastructure, and lack of human resource capacity.

Vital significance

The cost to the State of bulk supplies of second-generation antiretroviral drugs would be huge and has been the subject of fierce debate around the current preparedness for and pace of the drugs roll-out. This confers vital significance on the work of University of Cape Town medical graduate, Professor Michael Pepper, who recently joined the Witwatersrand School of Anatomical Sciences from the University of Geneva.

Pepper stirred major interest at a Roche Diagnostics In Vitro forum in Johannesburg in October by, among other things, suggesting that in the not too distant future a failure to genotype patients before any treatment could be considered unethical.

In his presentation, Pepper said that useful South African statistics for adverse drug reactions (ADR) were absent. However, in the USA 100 000 people died annually from ADR and more than two million hospital patients experienced ADR every year.

United Kingdom statistics showed ADR to be costing R3.8 billion per annum, with 7% of all patients affected.

ADR accounted for an estimated 10% of National Health Service (UK) bed days while chemotherapy ADRs increased overall drug costs by 15%.

Financial backing

At the time of writing, Roche Diagnostics were in the process of setting up a multi-million rand cutting-edge molecular diagnostics research platform for Pepper.

He is due to brush up on some technology in the USA before beginning his research in earnest this year.

It will be South Africa's first public-private partnership in this area. While genotyping and resistance testing is some way off, Pepper's current work centres on drug toxicity and therapeutic levels – how the patient metabolises the drug and the implications this has for medicine. He told the Johannesburg diagnostics forum that educating health care professionals about rapidly evolving molecular technology including the human genome was essential so that it could be incorporated into clinical practice as soon as practically possible.

Pepper told *Izindaba* that a great deal of work had been done on viral resistance, especially around relating mutations of the HIV genome directly to different kinds of drugs. However, 'very little' work around therapy had been done on the patient genome. Asked when he thought his work might begin to have direct benefit, Pepper said, with typical scientific caution, 'that's impossible to answer right now.'

He explained that sequencing the viral genome enabled scientists to tell whether a particular virus would become resistant. Mutations in the drug targets in the virus were predictors of whether there would be resistance or not. 'Practically, you take a blood sample and when you do the viral load you take some DNA from the virus and perform the sequencing in any one of a number of ways'.

Pepper said there had been 'enormous excitement at universities and in the public and private pathology sectors'. He said that two genes, the reverse transcriptase gene and the protease gene, underwent a large number of mutations, often in response to sub-optimal treatment, which conferred resistance to some of the AIDS drugs.

'These are the things we'd want to sequence and, depending on the mutations in these genes, we'd be able to predict to which drugs the virus would be resistant,' he said. This was done through algorithms that were constantly updated in public databases.

He added that the 'other side of the coin' was to examine the patient to see whether or not they would respond to antiretroviral and other drugs used in the treatment of the complications of AIDS. Many of these drugs, including antiretrovirals, caused severe and sometimes life-threatening side-effects.

Slow and fast metabolisers

People metabolise drugs at different rates. For slow metabolisers there could be a therapeutic effect but a greater risk of toxicity, whereas rapid metabolisers

might fail to achieve therapeutic levels while facing a negligible toxicity risk.

Pepper said work on the human genome would take far longer, 'because we don't yet know enough about the metabolism of antiretrovirals'.

Meanwhile Roche's AmpliChip CYP450 test, which analyses variations in two genes that play a major role in the metabolism of almost half of all drugs currently on the market, received the CE mark ('Conformité Européene'), allowing the test to be used for diagnostic purposes in the European Union.

The test detects genetic variations in the cytochrome P450 2D6 and 2C19 genes and provides the associated predictive phenotype (poor, intermediate, extensive, or ultra-rapid metaboliser). Results can be used by physicians as an aid for selecting drugs and individualising treatment doses for drugs primarily metabolised by the enzymes these genes encode.

Roche Diagnostics chief, Heino von Prondzynski, described the test as the first representative of an exciting new technology that held great potential for diagnostic applications.

The AmpliChip CYP450 test uses two industry gold standards, Roche polymerase chain reaction (PCR) amplification technology and Affymetrix high-density microarray technology (glass chips arrayed with tens of thousands of DNA fragments yet no bigger than a thumbnail). The latter's GeneChip System 3000Dx instrumentation, on which the AmpliChip is run, has also been CE marked.

Enzymes encoded by the CYP2D6 gene metabolise many antidepressants, antipsychotics, anti-arrhythmics, pain drugs, antiemetics, and beta-blockers (beta-adrenergic receptor blocker drugs). Enzymes encoded by the CYP2C19 gene metabolise drugs from a variety of classes, including anticonvulsants, proton pump inhibitors, anticoagulants, benzodiazepines, and antimalarials.

With AIDS, this new technology may only be useful for assessing the genetics of the patient's ability to metabolise antiretrovirals and other drugs used in the treatment of this disease.

Pepper said one indication of the 'Machiavellian nature' of HIV/AIDS, was that the virus mutated at a rate that was too quick for AmpliChip technology to be of use. The Chips were updated every 2 years, which did not allow for new mutations to be included in a timeous manner. He said other molecular techniques that could be adapted in a very short space of time to detect for novel mutations, would have to be used.

Pepper is a holder of the Walter Johnson award for post-doctoral research in cell biology (1974) and the prestigious Denber Pinard award for his Privat Docent Thesis (1977).

Chris Bateman

SHOT IN THE ARM FOR SAMA PUBLISHING

SAMA Secretary General, Dr Moji Mogare, signs the new HMPG deal with Cape Media founder, Andrew Fehrsen.

The departure of Peter Roberts, head of our Health and Medical Publishing Group (HMPG) this December after 20 years of forging it into a highly successful operation has become the catalyst for an exciting and creative realignment.

The core business of the HMPG is to produce 17 periodic medical publications in about 100 editions annually with content generation by a highly skilled and experienced editorial team. This team will remain directly accountable to the South African Medical Association (SAMA).

However, with some lateral thinking, a deal has emerged in which the HMPG business team (production, marketing, advertising, distribution) will partner Andrew Fehrsen, founder and MD of one of the country's largest business to business publishing houses, Cape Media.

Replacing institutional memory and specialist hands-on ability like that which Roberts has was never going to be an easy task, yet the current deal will open even more doors and optimise the HMPG operation.

Fehrsen, who has created over 100 jobs in Cape Media over the past 6 years, said at a ceremony to sign the

Cape Media founder and new HMPG partner, Andrew Fehrsen, with Deputy Editor of the SAMJ, *Professor JP van Niekerk.*