By Dr Tan Wu Meng, Editorial Board Member

Capturing Opportunities in Research

A Consultant at the Department of Haematology-Oncology, National University Hospital, **DR YONG WEI PENG's** research interests lie in the utility of pharmacogentics of anti-cancer agents and pharmacokinetic/pharmacodynamic modelling to rationalise cancer therapeutics in the Asian populations. His numerous awards include the NMRC-BMRC Clinician Scientist Investigator Award (Category B), the BMRC Research Grant, RISE/MAP award and NHG Small Innovative Grant.

TWM: You were in the news recently for the Clinician Scientist Investigator Award. How did you become involved in research? What were your formative research experiences?

Dr Yong: My research focus is in oncology, particularly in early phase clinical trials and in the area of pharmacogenetics. My first exposure to basic science research was in my 4th year of my medical school training. I spent four months of my elective training in a pathology laboratory in the British Columbia Cancer Agency in Vancouver. After graduating from Aberdeen University, I worked in an oncology unit in Aberdeen Royal Infirmary. Although not directly involved as an investigator, I was looking after patients participating in MRC (Medical Research Council) studies.

My formal research training began in National University Hospital. Our department encourages research, so we have some laboratory exposure very early in our fellowship training. I spent two years as part of the A*Star International Fellowship programme in Chicago. The clinical pharmacological fellowship, it was 70% research based, only 30% clinical. So that was where I got most of my training and exposure.

TWM: Who would you describe as your role models and heroes in clinical practice and research?

Dr Yong: In Singapore, I have to say that it is Dr Goh Boon Cher. He was also trained in Chicago and has single-handedly set up our early phase clinical trial unit. It is through his guidance that steered me towards pharmacogenetics.

My mentor overseas is Dr Mark Rattain. He was the person who guided me during my stay in Chicago.

TWM: Perhaps for the benefit of some of our readers who may not be as well-versed in the field, could you explain what pharmacogenetics is all about?

Dr Yong: Sure. The study of pharmacogenetics involves looking at how an individual's genetic makeup impacts on treatment outcomes. We can potentially use the knowledge and apply it clinically to help clinicians make therapeutic decisions such as what drug to use, what dose to give and whether we should avoid certain regimens.

Pharmacogenetics studies are usually incorporated into early phase clinical trials – Phase I and II – where you try to correlate differences in genetic makeup with treatment response, toxicity and pharmacokinetics parameter like drug level. From that you determine what are the genetic changes that are the important determinants to therapeutic endpoints or toxicities. These findings need to be validated in larger studies. Once validated, the pharmacogenetic knowledge can then be utilised in clinical settings.

TWM: From your experience, did you find that there were differences in pharmacokinetics between different communities?

Dr Yong: Yes. In fact one of the things that got us started is based on our observation that certain groups of patients have different treatment toxicity and efficacy results.

One example is warfarin. In terms of maintenance doses, often you hear anecdotal cases about how the Indian population needs a higher dose than the Chinese. Recently, we came to note that besides the CYP2C9, the metabolising enzyme for warfarin, there are evolving evidence that VKORC1 (Vitamin K epoxide reductase complex 1) haplotypes may influence warfarin requirement. Our group has established a model for predicting the maintenance dose of warfarin and we will be testing it out prospectively.

Now let us move on to cancer patients. In our previous study, we found that the Chinese population had more docetaxel induced myelosuppression compared to the Caucasian population. However, capillary leak syndromes were less commonly seen in the Asians. Currently we are engaged in a study to look at what are the important genetic determinants that might explain our observation.

TWM: Clearly you all have generated a lot of interesting ideas for your research but how do you go about generating a hypothesis? Is there a lot of serendipity involved? I think your latest paper talked about the pharmacokinetics of the drugs ketoconazole and

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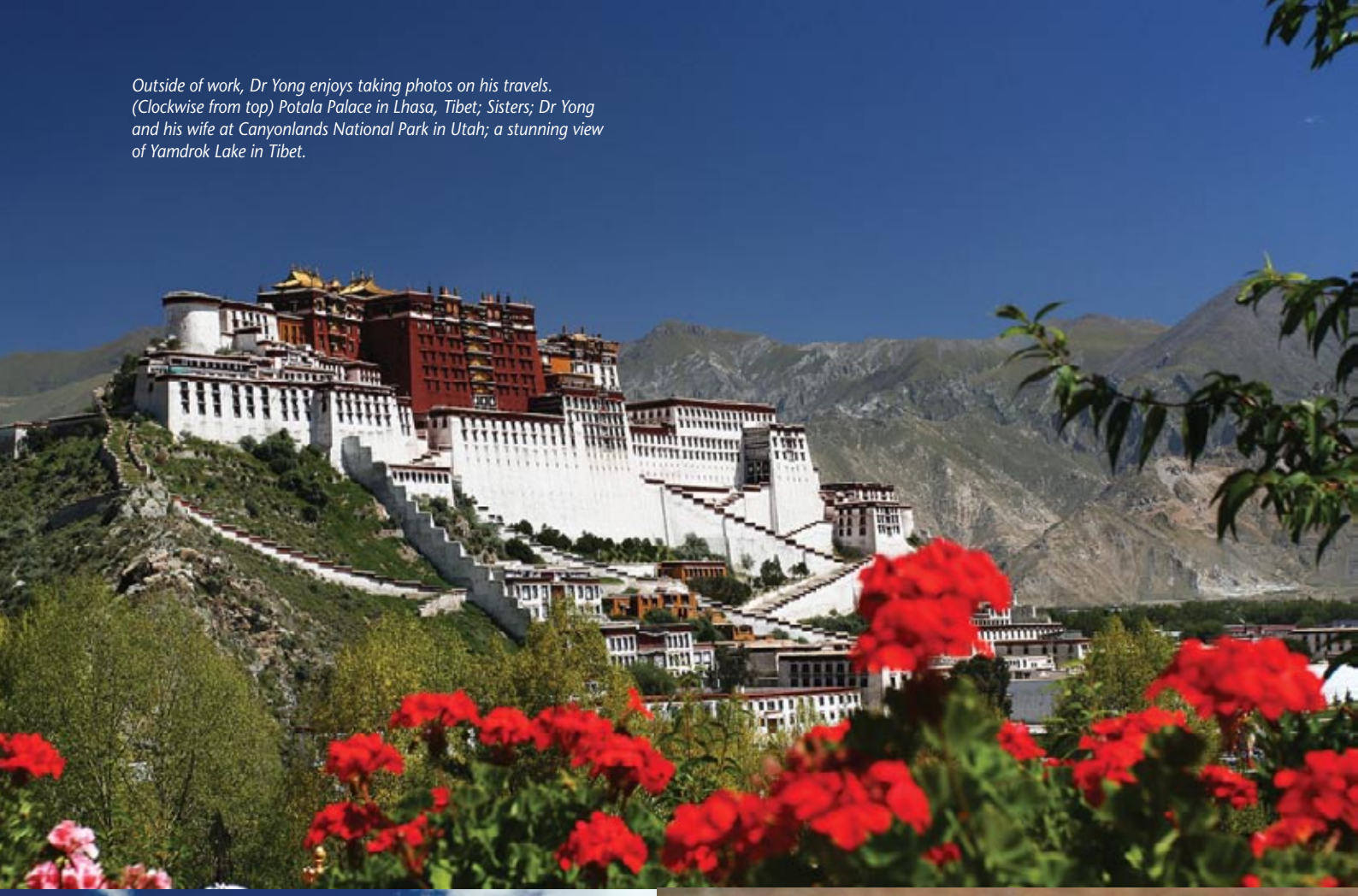
Outside of work, Dr Yong enjoys taking photos on his travels. (Clockwise from top) Potala Palace in Lhasa, Tibet; Sisters; Dr Yong and his wife at Canyonlands National Park in Utah; a stunning view of Yamdrok Lake in Tibet.



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etoposide. For those not in the field, the two seem quite unrelated – so what led you to that conclusion?

Dr Yong: Let me talk a little bit about those two drugs so that you all can have a better idea. Etoposide is an anti-cancer drug that is commonly used for small cell lung cancer, testicular cancer and numerous other cancer types, whereas ketoconazole is a very commonly used anti-fungal drug. Ketoconazole is a very potent inhibitor of cytochrome P450 3A4 enzyme and has earned a bad name because it can potentially interact with several drugs that are metabolised by CYP3A4 enzymes, including etoposide.

In this study, we hypothesise that the inhibition of cytochrome P450 3A4 would convert all the patients into poor etoposide metabolisers. We were hoping to use ketoconazole to reduce the amount of etoposide needed and the inter-individual variation in pharmacokinetics. From that study, as expected, we found that the systemic exposure of etoposide increased but unfortunately, we did not actually see a reduction in variability.

TWM: Moving on from the research of today to the research of tomorrow, do you feel our junior doctors, medical officers (MOs) and registrars have sufficient opportunities for research and does the existing system adequately recognise it?

Dr Yong: Probably not. Exposure to research is probably almost non-existent for junior doctors, except for individuals who have a lot of drive or initiative. This is understandable because their priority is first and foremost to receive adequate training to be a proficient clinician. Most of the time, research really starts during the fellowship (Registrar) training. I know that with regard to our cluster NHG, we have recently set up a Clinician Leadership programme that aims to offer participants training in research methodology and a one-to-one mentorship with an experienced researcher. There are now several start up grants available to young investigators. On the whole, the research atmosphere is getting more conducive.

TWM: What advice would you give a junior doctor who is aspiring to become a clinician investigator?

Dr Yong: Personally I feel a good mentor is essential. It is not easy without good guidance, especially for basic science research. If you can get someone to guide you, that would be extremely valuable. People who are interested should engage with others who have experience.

TWM: What kind of pitfalls would you warn a junior doctor who wants to do research to look out for, based on your own experience and what you have seen with other people doing research?

Dr Yong: Again, I think having a good mentor is essential. The most important part of a clinical study is probably in the study design. If a design is flawed, efforts spent in conducting the study will be wasted. Do not be afraid to seek help or collaborate with an experienced researcher.

My second advice for a budding clinician-scientist is to start with something small that you can really manage initially. Use start-up grant such as the NHG SIG (Small Innovative Grant) grants to fund pilot study. Generate preliminary data for future larger study. Once you get some good pilot results then you start aiming for larger grants like the NMRC (National Medical Research Council) grants.

TWM: What kind of additional infrastructure and institutional support would you advocate, if hospitals and healthcare clusters are to increase their breadth and depth of research?

Dr Yong: I would like to see provision for more laboratory space and increase collaboration between different healthcare clusters, and between basic scientists and clinicians.

TWM: Are there any types of integration or interaction that you personally feel would be beneficial?

Dr Yong: In the field of oncology, we are very lucky to have the infrastructural support of Oncology Research Institute – Translational Interface, an NUS initiative. The Institute provides a lot of technical help and core facilities for clinical researchers. The core facilities range from tissue preparation to genomics and proteomics analysis.

TWM: So to summarise, it is about getting core facilities so that people can leverage on that.

Dr Yong: Yes. It is about leverage on core facilities and maintaining interaction between clinical researchers and basic scientists. I think the Oncology Research Institute has actually done a fantastic job in terms of putting us at ease in working with them.

TWM: Do you ever see the day when research will ever become something like a blue letter service where you have an interesting idea but not necessarily the expertise – so you refer to someone in research and then they collaborate with you?

Dr Yong: In fact for research, most of the time is spent on talking, brainstorming and generating ideas, and not necessarily in the laboratory. Ideas often come through all these chatting. But I think a blue letter service may be a little bit far-fetched.

TWM: What do you personally see as the big research topics in oncology over the next 10 to 20 years?

Dr Yong: I think it would be individualised anti-cancer therapy. The improved understanding of tumour genomics has us realising that in fact, cancer is not a

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homogeneous single disease. Take breast cancer for example. Using gene expression assays, scientists have successfully grouped breast cancer into various subtypes where the behaviour and prognosis are very different. So certainly I think with improved understanding of the basic science on the tumour, we are able to use these knowledge to guide clinicians to select the most appropriate treatment for different individuals.

TWM: How would you compare the practice of oncology today with when you first started out as a fresh medical graduate? Has it changed even within that time?

Dr Yong: In Singapore, I see that the number of patients going for clinical trials has increased. Patients now have access to drugs that previously they may not be able to get. So that is certainly a huge change.

There is a huge change in the types of drugs used in medical oncology too, in terms of chemotherapy. Previously, the majority of our drugs were cytotoxic drugs. Now we see more usage of targeted agents. There is also increased awareness in the clinical utility of pharmacogenetics. The USFDA has recently included pharmacogenetic information in the package insert of three drugs, tamoxifen, irinotecan and 6-mercaptopurine.

TWM: It is still very early days but at the moment, what is the estimated cost to pharmacogenetic testing or profiling for a patient?

Dr Yong: This is a tough question because the cost constantly changes. Over the past few years, the price for genotyping has gone down tremendously. Obviously the issue of cost effectiveness will require further evaluation. The cost for invader® assay for UGT1A1 polymorphisms is approximately US$300.

TWM: Maybe just one or two last questions. Would you like to tell us about an interesting book that you have read?

Dr Yong: Well, not so recently read. It was a short story compilation called *Fancies and Goodnight* by John Collier, read in January this year.

TWM: What activities do you engage in outside of work?

Dr Yong: I am very interested in photography. I enjoy taking photos when I travel.

TWM: Thank you very much for your time. ■