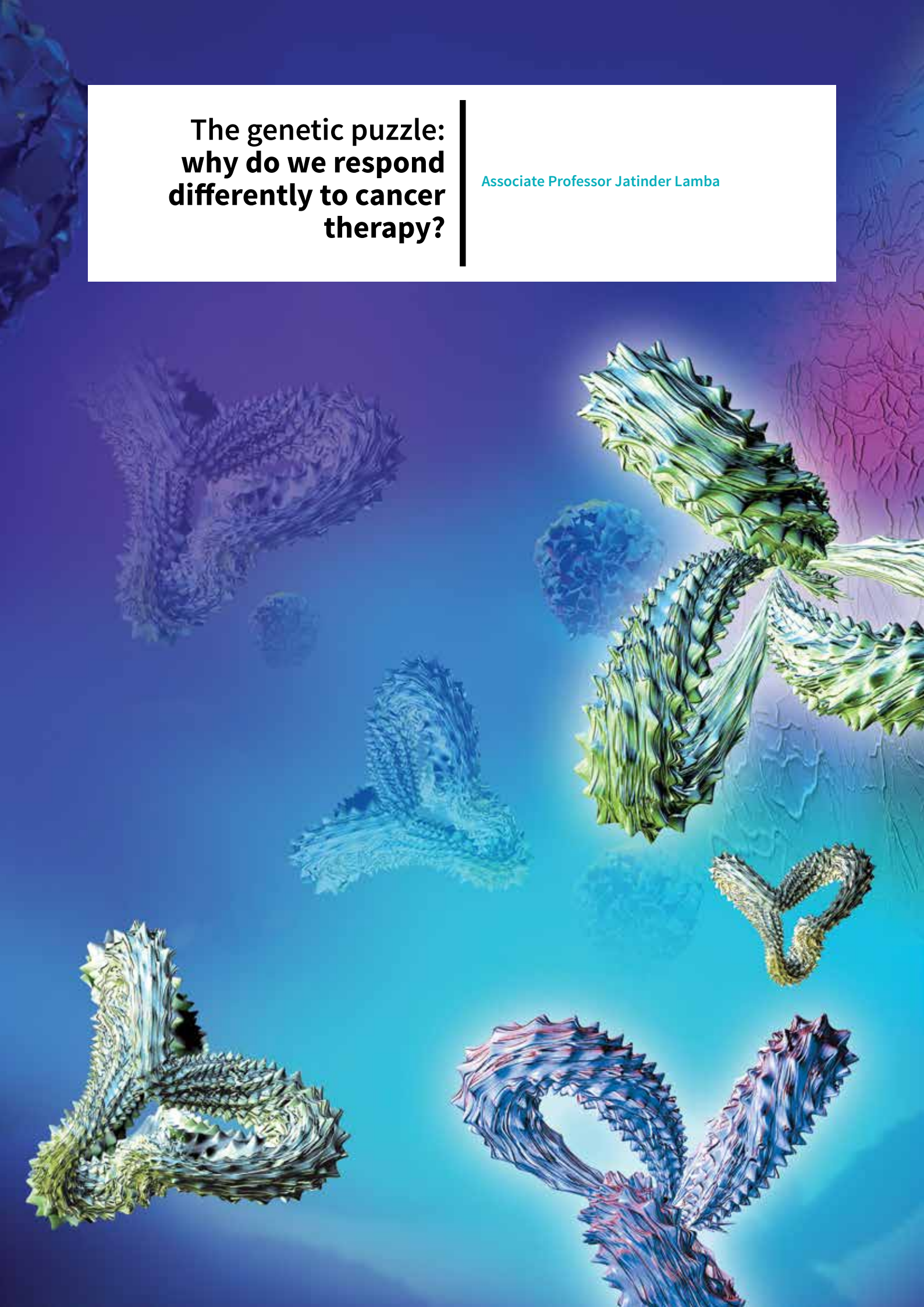
The genetic puzzle: why do we respond differently to cancer therapy?

Associate Professor Jatinder Lamba



THE GENETIC PUZZLE: WHY DO WE RESPOND DIFFERENTLY TO CANCER THERAPY?

Professor Jatinder Lamba, of the University of Florida, studies the genetic basis for inter-individual variability in the response to drugs, and in particular in the response of patients with acute myeloid leukaemia to antibody therapies. Understanding the basis for this variability could help to tune treatments for personalised medicine.

Variable responses to drug therapy

Why do some patients respond well to certain drugs, and get better, while others show no response, demonstrate an adverse response or signs of drug overdose, all on the same dose of the same drug? How a given patient responds to a drug is due to a variety of factors, but in large part the basis for inter-patient variability lies in our genetic makeup. Studying the influence of our genes on drug responses is called Pharmacogenetics. This fascinating discipline seeks to understand what genetic polymorphisms result in a change in drug responses, and how these polymorphisms cause those changes. The effectiveness of a drug or the manifestation of side effects could be influenced by changes in a variety of systems that interact with the drug on its path from ingestion, to the site of action, and eventual excretion. These include such entities as the cell membranes and drug transporters therein that permit the drug to pass through on its way to the target site, the enzymes which break the drug down or convert it into an active form, or the drug target itself. In many cases, the genetic variants that produce changes in these systems are tiny, but can have life or death consequences in terms of a patient responding to life-saving cancer therapies, or having a life-threatening adverse reaction to a drug. Our genome comprises billions of nucleotide bases, which form the genetic code that encodes for our unique biological makeup. In conjunction with the environmental factors we are exposed to throughout our lives, our genome determines so much about us, including the colour of our eyes, our height, and whether we will respond to a cancer therapy. A genetic variant causing a change in just one of those nucleotide bases, termed a single nucleotide polymorphism, can potentially result in a significant change in our drug responses, provided it occurs at the right location in the genome. Discovering where these locations are, and what effect a given single nucleotide polymorphism will have on the response to a certain drug forms the basis of the research of Professor Jatinder Lamba. In this article, we look at the results her team have produced to date, discuss her motivations for this type of research and her future plans.

Professor Lamba's motivations for pharmacogenetic research

Professor Lamba studies single nucleotide polymorphisms, which affect drug responses to acute myeloid leukaemia. She tells Scientia how she became interested in such research: 'My graduate research was focused on understanding how genetic differences impact patients' responses to drugs. At that time, the field of pharmacogenetics was in its infancy and I was really intrigued by how the genetic makeup of a person can influence therapeutic response or occurrence of adverse events in a patient.' She explains how personal motivations initially influenced her decision to get more involved with research into variability in drug responses: 'My interest grew stronger when I observed that my dad was not responding well to one of the hypertension medications he was taking and had to switch it due to certain side effects. This is a very common observation, not every patient responds to prescription drugs in the same way, yet for a particular disease, all patients are treated uniformly.' Eventually, her focus moved to acute myeloid leukaemia:

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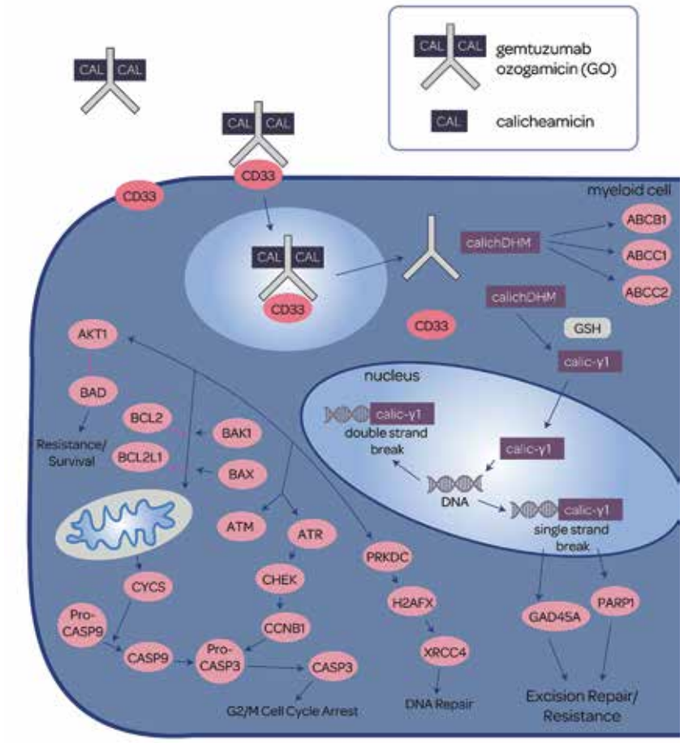

'I moved to St. Jude Children's Research Hospital in 2000 for my postdoctoral training, where state of the art research in the area of precision medicine to improve treatment outcomes in children with cancer was being carried out. Research in last decade or so for childhood acute lymphoblastic leukaemia has resulted in improving 5-year overall survival, so that it now lies at over 90%. However, such an improvement has not yet been observed in acute myeloid leukaemia and being at St. Jude and seeing kids in the hospital inspired me to focus my research on this disease. I wanted to scientifically contribute to enhance our understanding of acute myeloid leukaemia as well as interpatient differences in drug responses and the development of drug resistance. My current research is focused on all these areas in acute myeloid leukaemia and I am hopeful that our results will be utilised in clinics to design personalised therapeutic strategies to improve treatment outcomes.'

Acute myeloid leukaemia and antibody therapies

Leukaemia is a cancer that results in a rapid growth of abnormal white blood cells and normally begins in the bone marrow. Acute myeloid leukaemia is a leukaemia subtype. The intense proliferation of the abnormal white blood cells is usually coupled with a drop in other types of blood cells. Common symptoms include fatigue and paleness, as a result of a drop in red blood cells. Patients may also have a greater susceptibility to infection due to a drop in normal white blood cells and an increase in abnormal white blood cells, which have no ability to fight infection. Leukaemia patients may also have a greater propensity for bleeding and bruising. Currently, the 5-year survival rate for acute myeloid leukaemia in adult patients is approximately 27%, which highlights the difficulties clinicians and scientists face in establishing effective treatments for this disease. Professor Lamba discussed the poor prognosis of acute myeloid leukaemia patients with Scientia: 'Acute myeloid leukaemia has a dismal outcome. In spite of advances made in the past decade, the overall survival is not great for these patients. There is an urgent need to develop therapeutic strategies which incorporate new drugs as well as design chemotherapeutic regimens using a patient's genome in conjunction with disease characteristics to achieve maximum treatment benefit.' A particularly promising therapeutic approach involves the use of cytotoxic agents that can kill leukaemia cells, coupled with monoclonal antibodies, which are protein structures that can bind with great specificity to biological targets. The concept involves attaching a cytotoxic agent to a monoclonal antibody that is specific to a protein target present on leukaemia cells. This can enable the drug conjugate to preferentially bind to the cancer cells, enhancing the effectiveness of the cytotoxic drug and preventing it from producing off-target side effects elsewhere in the body. One such example is gemtuzumab ozogamicin, which combines the cytotoxin calicheamicin with a monoclonal antibody specific for CD33, a target on the surface of the leukaemia cells of 85–90% of all patients with acute myeloid leukaemia. The drug conjugate causes breaks in DNA in treated cells, which lead to cell death. The antibody-drug conjugate must bind to CD33, whereupon it is taken into the cell, in order to exert its effects. Given that the vast majority of acute myeloid leukaemia patients express the CD33 target, one might imagine that this drug combination would be highly effective in almost all patients. However, inter-individual variability means that this is not the case.

Inter-individual variability in acute myeloid leukaemia – results to date

Gemtuzumab ozogamicin has been shown to improve survival of a subset of newly diagnosed patients with acute myeloid leukaemia. However, there is significant

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variability in patient responses to this drug. For example, it is effective in only one quarter of patients who have previously relapsed, when used as a single agent. The reasons underlying this variability remain poorly understood. In order to begin to understand the genetic basis for this variability the team initially undertook a small pilot study involving the genetic analysis CD33 gene in genomic DNA from 22 paediatric patients with acute myeloid leukaemia, who were all treated with gemtuzumab ozogamicin. Interestingly, they found that a single nucleotide polymorphism in the gene encoding the drug target itself, CD33, was a predictor of drug response. The team concluded that the polymorphism could potentially affect how CD33 functions, which could interfere with gemtuzumab ozogamicin binding or the proteindrug complex internalisation into the leukaemia cells following drug binding.

Encouraged by these results the team planned and undertook a much larger study. This involved a larger clinical trial of 242 paediatric patients with acute myeloid leukaemia, who were treated with gemtuzumab ozogamicin, as part of a combination chemotherapeutic treatment. These patients were compared with 172 others, who were treated in a similar manner, but did not receive gemtuzumab ozogamicin. The team found several CD33 single nucleotide polymorphisms that correlated with improved outcomes in patients treated with gemtuzumab ozogamicin. For patients treated with gemtuzumab ozogamicin, who had two copies of one particular polymorphism, the 3-year overall survival rate from remission was 84% +/- 8% compared with 68% +/- 15% for other genotypes. In addition, these patients had a superior disease-free survival and a lower risk of relapse. Most recent results from Dr Lamba’s recent study in another cohort of ~1000 pediatric AML patients, 500 of whom received standard therapy and 500 received gemtuzumab ozogamicin along with standard therapy again confirmed that CD33 polymorphisms can be used as biomarkers to identify patients who will or will not benefit from addition of gentuzumab to chemotherapy. Using this information can help in designing the most effective chemotherapeutic regimen based on a patient’s genetics and identifying patients who should or should not be given gemtuzumab.

Future work

The value of being able to predict patient responses to gemtuzumab ozogamicin, through a simple genetic test would be immense. The results of such a test could help patients and their physicians to better plan their treatment. It would also help to manage patient expectations about treatment outcomes. One of the most valuable aspects of accurate treatment outcome predictions, using simple genetic testing, is the avoidance of exposing patients who are unlikely to benefit from a given treatment to unnecessary toxicity and wasted time that could be spent on treatment opportunities elsewhere. Conversely, identifying which patients will most benefit from a given treatment could greatly enhance treatment outcomes. In their future research, the team wish to identify single nucleotide polymorphisms which are indicative of treatment response in acute myeloid leukaemia. They are particularly interested in genes involved in cell death, DNA damage, DNA repair and detoxification enzymes. Professor Lamba talked to Scientia about her hopes for future research, in terms of clinical translation of these valuable results: ‘The next steps involve moving the genetic testing to clinics and developing personalised therapeutic approaches. We are also looking forward to using the results from our research to develop novel therapeutic agents of relevance to acute myeloid leukaemia.’

Meet the researcher

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Professor Jatinder Lamba obtained her PhD from the Postgraduate Institute of Medical Education and Research, Chandigarh, India on the ‘Pharmacogenetics of CYP2C19 in North Indians’, following which she pursued postdoctoral research in the USA at St. Jude Children’s Research Hospital, Memphis, Tennessee. She is currently an Associate Professor (with Tenure), Preeminent Scholar and the Graduate Program Coordinator in the Department of Pharmacotherapy and Translational Research in the College of Pharmacy at the University of Florida. She is the Chair of the Pharmacogenomics Focus Group of the American Association of Pharmaceutical Scientists and is an author on over 70 journal articles and two book chapters.

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