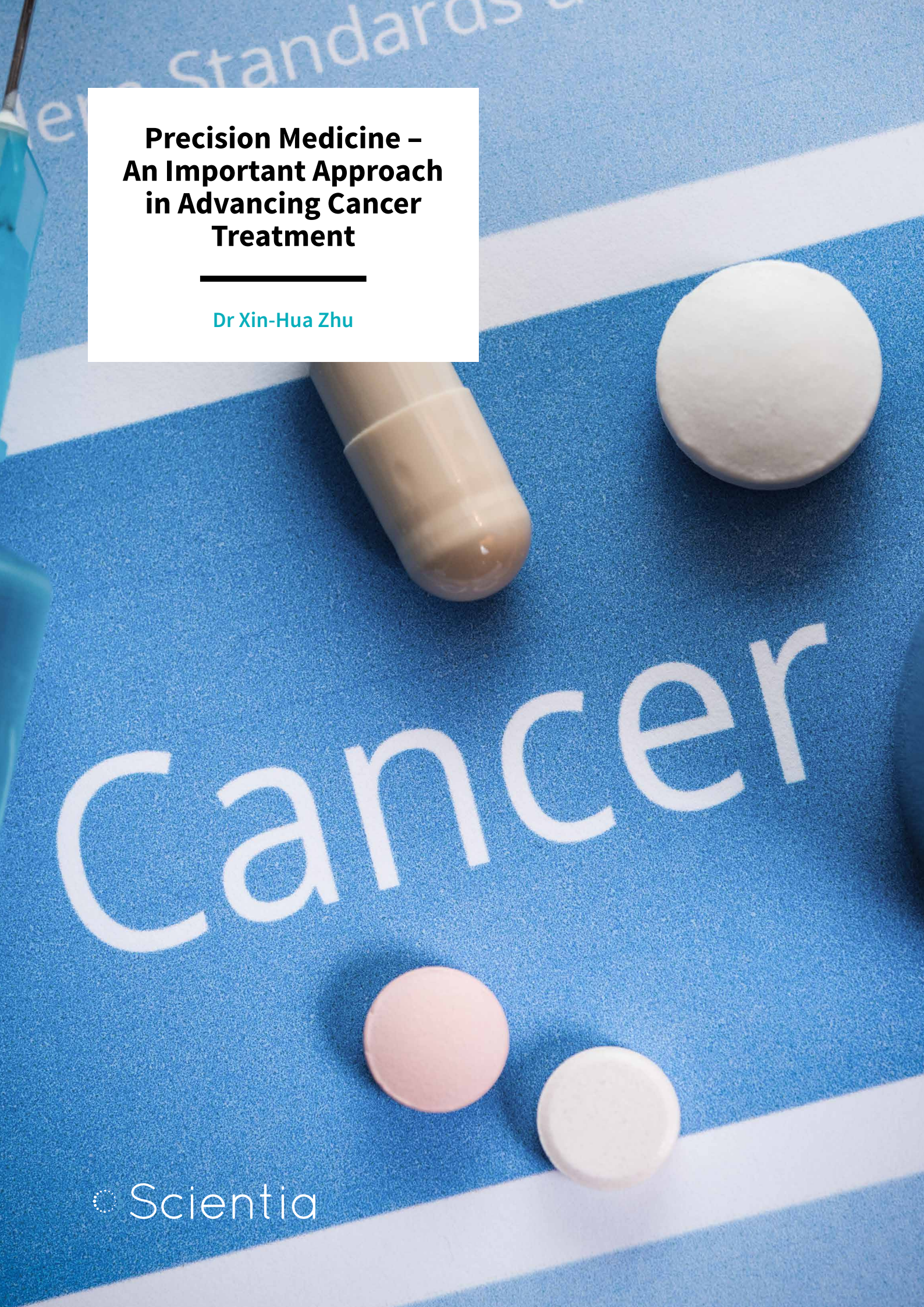
Precision Medicine – An Important Approach in Advancing Cancer Treatment

Dr Xin-Hua Zhu



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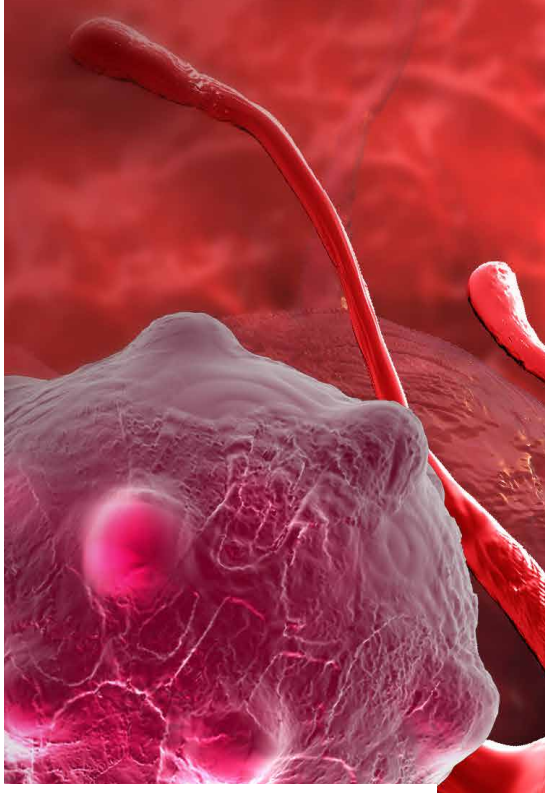
PRECISION MEDICINE – AN IMPORTANT APPROACH IN ADVANCING CANCER TREATMENT

In precision medicine, disease prevention and treatments are specifically tailored to each individual patient, taking into account their genetics and physical function. For individuals with cancer, clinicians can carry out genomic testing to identify key markers that can be targeted for treatment. While advances in medicine mean that precision medicine has become more accessible, the efficacy of the approach in cancer remains unclear. **Dr Xin-Hua Zhu** at the Zucker School of Medicine at Hofstra/Northwell is committed to providing definitive answers as to how best we can use precision medicine in cancer treatment.



Cancer Treatment – One Size Does Not Fit All

There are more than 200 types of cancer that can be found in different organs and originate from different cell types. Despite this complexity and variability, cancer treatment plans tend to take a 'one size fits all' approach, with everyone with the same cancer type receiving a combination of the standard four treatments: surgery, radiation therapy, chemotherapy and immunotherapy.

Through years of accumulated knowledge in cancer research, we now know that cancers are highly heterogeneous. This means that any particular cancer will most likely not be exactly the same as that of someone else who has cancer, even in the same organ of their body. Thus, not all patients with the same cancer type will respond the same way to treatments, and any particular class of cancer drug can be ineffective in an estimated 75% of patients. Non-responders to cancer treatment often suffer from unnecessary adverse effects as a result of treatment and of course, inherent to this is also a delay in progression to an effective treatment.

Precision medicine aims to deliver a more targeted treatment. A sample taken from a patient's tumour will be sent off to have the genome 'read' in a process known as genomic sequencing. Then, identification of the genomic changes (aberrations) of tumour cells allows researchers to identify potentially actionable information to help guide treatment decisions. With breakthroughs in our understanding of which genomic changes can drive tumour growth, we are now able to identify 'driver mutations' by using the widely available technique known as next-generation sequencing. Understanding this background for each patient facilitates a more targeted approach in which aberrations in the genomic profile of a tumour can be targeted to reduce aspects such as growth rate and also help induce tumour cell death.

Although genomic testing allows for an in-depth examination of the genomic profile of a tumour and its aberrations, factors such as physical function, the type of cancer, how big it is and whether it has spread to other locations in the body also play a part in determining treatment options. This multifactorial tailoring in treatments means, in theory, that there will be a reduction in the number of patients going through treatments that will not be effective for them as a result of their cancer type associated with the genetic background. Optimising tumour response, taking into account the therapy-induced toxicities for each specific patient and combining optimised tumour response with the preservation of organ function

will help to maintain the quality of life for patients undergoing treatment. However, before this is possible across the board for all cancer patients, further work is needed in identifying biomarkers and matching these with effective treatments.

Moving Precision Medicine Forwards

Many factors have led to precision medicine becoming an increasingly popular and accessible option in clinical practice. These include an increased understanding of driver mutations, the accessibility of genomic testing for patients, and the development of more targeted treatment options. Over the past decade, several key precision medicine approaches have emerged with targets including neurotrophic receptor tyrosine kinase (NTRK) gene fusions, microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) and tumour mutation burden-high (TMB-H) used to select therapies regardless of the tumour origin.

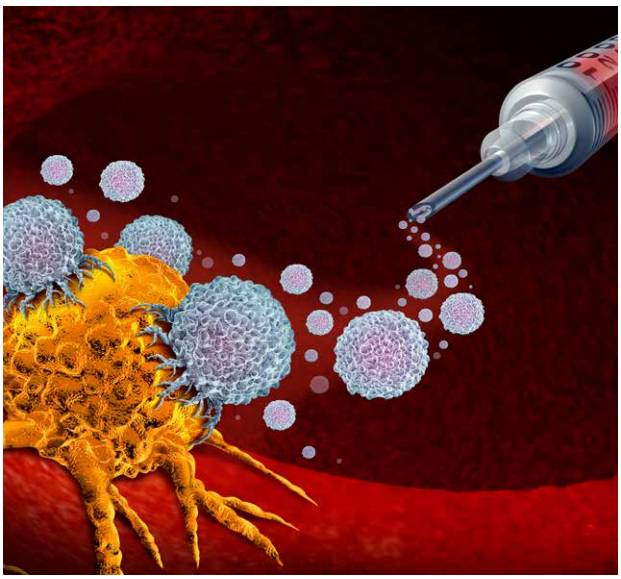
The discovery of these biomarkers as therapeutic targets has resulted in the development of treatments such as NTRK blockers (e.g., larotrectinib and entrectinib), microsatellite instability, and MSI-H or dMMR or TMB-H with pembrolizumab (programmed death 1 (PD-1) blocker). These are all USA Food and Drug Administration-approved drugs for patients who test positive for these biomarkers.

The biomarkers identified as having targetable treatments are epidermal growth factor receptor, anaplastic lymphoma kinase fusion, B type Raf kinase mutation, PD-1, KRAS G12C mutation, ROS1 rearrangement, RET rearrangement and MET mutation in non-small cell lung cancer, HER2 amplification, PIK3CA mutation and ESR1 mutation for breast cancer.

Dr Xin-Hua Zhu at the Zucker School of Medicine at Hofstra/Northwell is pushing forward the field of precision medicine by identifying biomarkers and exploring the associated treatment options in mixed cancer types, bladder, and renal cancers. His approach to highlighting potential biomarkers for targeted treatment differs from other research in that he combines messenger ribonucleic acid (mRNA) and microRNA (miRNA) expression results to gain an overall picture of gene expression. Importantly, mRNA represents the differential expression of genes and miRNA can act as an oncogene or a tumour suppressor gene, with the capability to promote or suppress cancer development.

Examining the expression of both mRNA and miRNA allows for the detection of how highly they are expressed in the tumour cells, meaning that highly expressed or downregulated 'driver' genes can be identified as potential therapeutic targets.

Dr Zhu's initial work involved a retrospective study of 652 patients, across 10 different cancer types, 135 of whom received targeted therapy as a result of biomarker testing. Here, the most common alterations in the tumours were KRAS, PI3K and BRAF followed by PD-1/PD-L1. They found that 23.5% of the patients who received targeted therapy had a partial response rate, 17.6% resulted in stable disease and the disease control rate was 41.1%. These promising results suggested a clear potential for precision medicine in real-world community oncology practice, and warranting further large and prospective studies in patients with targetable biomarkers regardless of tumour origin.



Dr Zhu then completed studies in muscle invasive bladder cancer and in doing so, contributed significantly to the growing school of thought proposing a vital role of mitochondrial response genes, DNA replication genes and DNA damage genes in differentiating response versus non-response to neoadjuvant chemotherapy (NAC). Previous studies had shown that p53-like tumours are mostly resistant to NAC – a finding that was later backed up by Dr Zhu's study in 2022, in which 90% of patients who did not respond to NAC were also found to have p53-like tumours. This is consistent with the known profile of the p53 signalling pathway which monitors DNA replication and cell division, and responds to intrinsic and extrinsic stress signals. This also suggested the potential for this pathway as a therapeutic target.

Further research by Dr Zhu has focussed on investigating potential genes involved in metastasis in stage I and II patients – in particular, clear cell renal cell carcinomas (ccRCC). Research into metastatic cancer therapies is particularly important in precision medicine, as once a tumour has metastasised (appeared elsewhere in the body away from the primary tumour site), treatment becomes much more difficult. Dr Zhu's work identifying the molecular signatures of more aggressive tumours in clinically low-risk ccRCC patients should allow for gaining a better understanding of the future metastatic potential of tumours and thus, shape the proposed treatment strategy.

Problems with Precision Medicine

Although this is an exciting field of research, precision medicine does not come without some frustrations and dilemmas. Cancer, by nature, evolves over time and even after treatment. As such, implementing a full precision medicine treatment plan after diagnosis could require multiple rounds of genomic testing between each treatment type – an expensive and time-consuming process.

Alongside this, our knowledge of targetable biomarkers and matched treatments, whilst much improved compared to 10 years ago, is still not at a point where we fully understand the possible impacts of this approach. Even carrying out clinical trials in this area can be difficult, as clinical trials are often carried out in patients whose disease has progressed after the available standard of care has been provided. The condition of these patients can deteriorate rapidly, leading them to leave trials early or before testing results have been returned and the patient moved to hospice care. In addition to this, clinical trials in this area often involve only a small number of patients, and therefore, are not always fully representative of the true patient population.

When it comes to implementing precision medicine clinically, multiple targetable drugs are often available for patients based on their genetic background. This can result in a lack of clarity around the selection of the 'best option' for patients going forwards – a factor that is exacerbated by many physicians having low confidence in their knowledge of gene functions. However, further research in this area to improve our knowledge will likely lead to improved identification of treatments for patients and wider recognition of the possible options that clinicians may offer.

A Brighter Future Lies Ahead

Despite these difficulties, an increase in the knowledge and resources that precision medicine can offer has the huge potential to increase the effectiveness of cancer treatment plans. Already, improved patient response rates and progression-free survival have been seen in early-stage clinical trials that have used biomarkers to select patients. Nonetheless, there is still a long way to go before precision medicine becomes fully embraced, and a coordinated effort between researchers, pharmaceutical companies, regulators, clinicians and patients is needed to drive this emerging but important field forward.

Meet the researcher

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Dr Xin-Hua Zhu is a physician-scientist holding both an MD (Soochow University Medical College, China) and PhD (Shanghai Jiao Tong University School of Medicine, China). He completed his postdoctoral training at Memorial Sloan Kettering Cancer Center and is currently an Associate Professor at Donald and BarbaraZucker School of Medicine at Hofstra/Northwell. Dr Zhu is board-certified in internal medicine, haematology and medical oncology. He completed his residency in Internal Medicine at Mount Sinai Medical Center and also completed a Hematology and Medical Oncology Fellowship at New York University Langone Medical Center. His work is dedicated to the treatment of genitourinary and cancers and in particular, identifying biomarkers for renal, bladder, pancreatic and prostate cancer. Dr Zhu is an active member of the American Association for Cancer Research, the American Society of Clinical Oncology, and the American Society of Hematology and has received some funding to support his vital research.

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https://feinstein.northwell.edu/institutes-researchers/our-researchers/xinhua-zhu-md-phd

FUNDING

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FURTHER READING

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