Testing the cardiotoxic effect of cancer therapies with micro-hearts

Cardiovascular dysfunction following cancer treatment greatly impacts the quality of life of cancer survivors. **Dr Tetsuro Wakatsuki** and his colleagues from InvivoSciences Inc. aim to develop therapeutic solutions to this problem, by exploring the cardiotoxic effects of novel anticancer drugs using pioneering technology, such as 3D-engineered micro heart tissue.

Every 30 seconds in the United States a person is diagnosed with cancer. However, despite this depressing statistic, more people than ever are surviving the disease. Today, two out of every three patients are expected to live at least five years following their diagnosis, which corresponds to approximately 14.5 million cancer survivors in the US alone. For example, in the 1980s, the chance of surviving from breast cancer was 50:50, but now nearly 80% of patients survive. This is due to extensive research which has improved early detection, therapy and medication development.

However, length of survival is variable and depends on several factors, including tumour severity, the patient's general fitness and the impact of treatment-related chronic diseases: chronic diseases, such as cardiomyopathy which affects the heart muscle, that arise as a result of treatment.

CANCER TREATMENT-RELATED CARDIAC DYSFUNCTION

Intensive cancer treatments can unfortunately have an adverse cardiovascular impact. For example, chemotherapy greatly weakens the heart muscle, and radiation results in cardiotoxic effects such as heart inflammation, atherosclerosis and rhythm disorders. Anticancer medication such as tyrosine kinase inhibitors (which suppress cancer cell growth), can also induce cardiomyocyte apoptosis, hypertension and congestive heart failure. Angiogenesis inhibitors (which suppress blood vessel formation, thus isolating cancerous cells and inhibiting their spread) can also cause hypertension, increasing the risk of blood clots and heart failure.

In fact, cancer-treatment-related cardiotoxicity is the third leading cause of therapy-associated mortality in cancer patients. Clearly, this severely impacts quality of life both physically and mentally – after all, it must be devastating for the cancer survivor to discover that they have another life-debilitating disease.

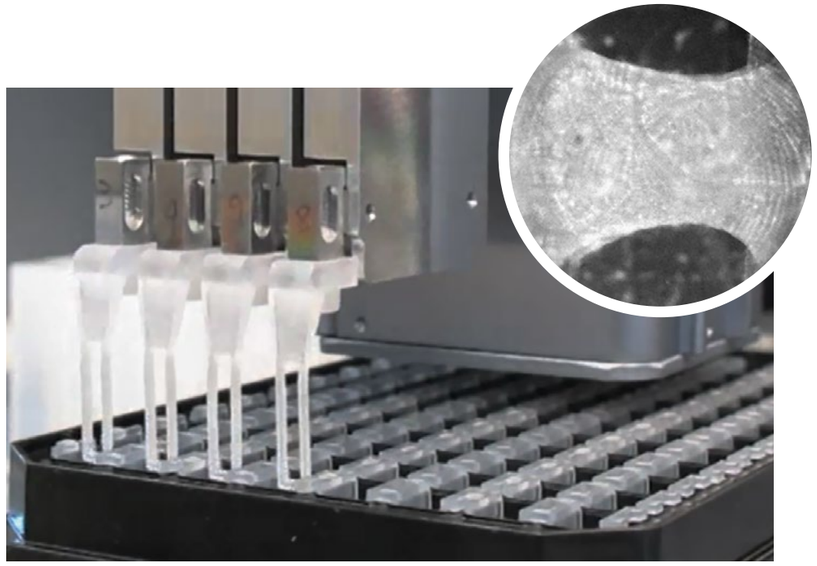
CARDIO-ONCOLOGY

Growing concern regarding cancer/cardiotoxicity comorbidity has led to the development of a novel clinical discipline – cardio-oncology. The aim of this emerging field is to investigate the physiological mechanisms that cause cardiovascular disorders in patients undergoing cancer treatment, to improve detection and prevention of these heart defects and

Cardio-oncologists face many challenges. There is a shortage of hospital funding; a lack of training opportunities; limited awareness; and inadequate research relating to the relationship between cancer, therapies and the heart

develop effective treatments. It is also essential that a balance is established between cancer elimination and cardiovascular protection.

However, cardio-oncologists face many challenges, mainly due to the novelty of the field. For example, there is a shortage of hospital funding to develop cardio-oncology units; a lack of opportunities for education and training; limited awareness regarding cardio-oncology; and inadequate research relating to the relationship between cancer, therapies and the heart. Most importantly there is no simple diagnostic tool to monitor the severity of cardiovascular damage caused by cancer treatment.



Reconstituted 3D human heart tissues, NuHeart™, in 96-well plate undergoing a mechanical testing with Palpator ™ device
Cutout: a close-up of the tissue itself

INVIVOSCIENCES

InvivoSciences (IVS), established in 2001, aims to tackle these problems. The ground-breaking research of Dr Wakatsuki and his colleagues explores potential solutions to cardiovascular issues, using innovative cardiac safety assessments. The team at IVS use their award-winning technology – laboratory-made human micro heart tissue called NuHeart™ – to test the effects of potential new anticancer drugs on cardiac safety. According to the U.S. Food and Drug Administration (FDA), effective drugs which have minimum impact on heart health should be used as a first-line treatment option to newly diagnosed cancer patients.

Induced pluripotent stem cells (iPSC) are the foundation of all the technological services that IVS offers. Patient-specific adult cells in blood, or even urine, samples can be reprogrammed into a pluripotent state. This means that the cell has the potential to differentiate into many different cell types in the body, including cardiomyocytes in the heart.

In collaboration with the FDA National Center for Toxicological Research (NCTR) in Jefferson, Arkansas, a cost-effective and rapid assay was performed: this involved cardiotoxicity analysis of all 31 anticancer drugs belonging to a class called kinase inhibitors using human iSPC cardiomyocytes cultivated in micro-well plates. The preliminary data highlighted that different levels and types of cardiotoxicity generated by the kinase inhibitors can be seen *in vitro* and correlate well with some clinical observations, suggesting thorough studies with 3D engineered micro heart tissue should further confirm the observations.

3D ENGINEERED HEART TISSUE DEVELOPMENT

The Research Team at IVS then took this research further to grow engineered micro heart tissue. Amazingly, these micro-hearts (see above image) can beat for weeks, even months. Micro human heart tissues are a significantly more predictive preclinical tool, compared to immature cardiomyocytes cultured on plates. Cells mature in a 3D tissue environment and mimic functions of healthy or diseased heart tissues, allowing the researchers to explore the physiological and pathological mechanisms underpinning both states. Because patient-derived organs and tissues can be reconstituted in micro wells, ultimately, the 3D micro tissue technology will bridge the gap between cell-based assays and clinical studies. Furthermore, this novel technology promotes personalised medicine: patient-specific cells obtained from blood samples can be used to generate heart cells, which are then used to grow micro-hearts, NuHeart™. Therefore, patient-unique responses to new drug candidates can be explored.

The primary focus of the IVS team is to study dose-dependent effects of new anticancer compounds on a range of cardiovascular-specific physiological mechanisms. These include oxidative stress, mitochondria dysfunction, excitation-contraction coupling, contraction duration, ion channel interference (regulators of heart rhythm) and damage of contractile structures. Drugs that display no, or little, cardio-safety risk move forwards in the testing process and are one step further toward commercialisation. Alternatively, compounds that do threaten heart health are further analysed and can sometimes be modified to improve their cardiotoxicity profile. Furthermore, the tool is being used to identify smart diagnostic tools for cardio-oncologists to monitor a patients' heart condition that has been affected by anti-cancer drugs.

CLINICAL ADVANCES

Overall, the field of cardio-oncology has raised awareness of the cardiovascular risks of cancer therapy. Recently, the American Society of Clinical Oncology (ASCO) have proposed a set of guidelines for clinicians to follow to reduce the risk of cancer patients suffering from cardiovascular myopathy during/following treatment, by identifying risk factors in patients vulnerable to cardiovascular injury. These include obesity, smoking, diabetes, hypertension and high-dose radiotherapy where the heart is in the treatment field. ASCO also emphasise the importance of performing regular echocardiograms/cardio MRIs during each stage of clinical care, to monitor cardiovascular activity.

Interestingly, biomarkers, such as troponin, can also be used to identify early stages of cardiovascular dysfunction, before symptoms appear. Troponin, composed of three regulatory proteins, is essential for cardiac muscle contraction. Following cardiomyocyte damage, troponin is released and consequently is regarded as a highly efficient indicator of cardiotoxicity.

Early detection of cardiovascular dysfunction ultimately means early treatment. Research has shown that some heart diseases triggered by anticancer drugs can be treated using common heart medications. However, the overall goal is to prevent cardiovascular damage in the first place. By identifying novel anticancer drugs that could compromise cardiac safety, Dr Wakatsuki and the team at IVS are taking science one step further to achieving this goal.

By identifying novel anticancer drugs that could compromise cardiac safety, the team at InvivoSciences are taking science one step further to detecting cardiovascular dysfunction earlier

Q&A

Why do different cancer treatments result in cardiovascular dysfunction?

There are two different reasons; one is on-target and the other is off-target effect. Any drugs are potentially toxic, especially the anti-cancer drugs designed to kill rapidly growing cells. Recent smarter drugs only target abnormally active and growing cells, i.e., cancer cells. Therefore, those targeted therapies are much less toxic and effective at killing only cancer cells. However, some of the proteins need to be active to the physiology of the cardiovascular system, including the heart. The cardiovascular system carries those drugs and it can therefore become damaged. The heart is one of the most sensitive organs to drug toxicity.

How can 3D-engineered micro heart tissue be used to further our knowledge about cardiotoxicity?

Immature cardiomyocytes are more sensitive to proarrhythmic drugs. If the toxicity test is too sensitive, potentially useful drug candidates may not move forward to the drug discovery pathway. The micro 3D heart tissue is one of the ways to attain many mature cardiomyocytes cost-effectively for testing drugs.

Can your technology be applied to clinical issues other than cardiovascular myopathies?

This technology can reconstitute 3D tissues for different organs and tissues. Our 3D cell culture technology is designed to grow "Tissue Strip". A tissue strip spans between solid structures like skeletal muscle attaching to bones, or skin covering bones or blood vessels, or stomach or heart enclosing biofluid and withstanding its pressure. We have applied this technology to fabricate skin, blood vessels, and skeletal muscles. There are so many orphan diseases (rare diseases affecting low numbers of people) with known and unknown mechanisms affecting those types of organs and tissues.

What are your future research goals?

For the cardio-oncology project, we need to continue the analysis of 31 kinase inhibitors and other target cancer therapies using cells and micro-heart tissues. The data need to be correlated systematically to the data obtained clinically to determine off- or on- target effects for further understanding of the toxicity mechanisms. The clinical data need to be organised more systematically, based on parameters that can categorise cardiotoxicity quantitatively. These data from pre-clinical testing and clinic trials can improve our understanding of the mechanism of anti-cancer-drug-induced cardiotoxicity. So, we can develop new approaches to reduce cardiotoxicity while maximising the efficacy of cancer treatment for the cure and healthy survival of cancer patients.

Detail

RESEARCH OBJECTIVES

Dr Wakatsuki's research focuses on 3D engineered micro heart tissues and their applications to issues seen during and after cancer treatments. He is the co-founder of InvivoSciences – a company whose research provides solutions to cardiac issues.

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COLLABORATORS

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BIO

Dr Wakatsuki studied for his PhD in BioPhysics and MS in Mechanical Engineering both at Washington University. He later went on to work as Assistant Professor at the Physiology, Biotechnology and Bioengineering Center at the Medical College of Wisconsin before starting full-time at InvivoSciences, where he currently works as the Co-Founder and Chief Scientific Officer.

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