DR JIAJIU SHAW

Solving the side effects of chemotherapy

Medicinal chemist and cancer researcher **Dr JiaJiu Shaw** discusses the need to develop novel chemoprotective agents, and shares the details of his own work towards accomplishing this goal

Could you introduce your current research project entitled 'Novel small-molecule TNF modulators as chemoprotective agents'? What are its chief aims and mission?

In this project, we aim to show that UTL-5g protects tissues from chemotherapy-induced side effects. We started by examining the protective effects of UTL-5g on nephrotoxicity, hepatotoxicity and myelotoxicity on cisplatin. With the current successful data, we are beginning to expand our research to investigate whether UTL-5g protects tissues against oxaliplatin. We may even examine additional anticancer therapeutics.

Your project focuses on the tumour necrosis factor alpha (TNF-α) inhibitor, UTL-5g. Why was UTL-4 unacceptable as a chemoprotective agent?

UTL-4 compounds are the predecessors of UTL-5 compounds. Although UTL-4 compounds display significant anti-inflammatory properties, their IC50 values are similar to that of leflunomide, which is known to be associated with several potential side effects. This is why we did not conduct many chemoprotective studies on UTL-4 compounds. One of the main reasons we pursued UTL-5g as a chemoprotector is that most of the UTL-5 compounds are associated with very low acute toxicity and UTL-5g shows the highest potency among them.

What are the benefits of taking a collaborative approach to your project? In particular, how did your collaborations with Drs Frederick Valeriote and Ben Chen help move your study in the right direction?

Dr Valeriote has more than 35 years of experience in cancer research. He also has extensive research experience in radioprotection, which is another potential application of UTL-5g. Dr Chen has over 30 years of research experience in immunology and haematology; both related areas of chemoprotection and radioprotection. Their collaborative efforts are critical to my continued productive research progress. Of course, there are also many other collaborators and supporters that I have to be thankful for.

Will there be any wider benefits to the development of UTL-5g?

Yes, as I mentioned briefly, UTL-5g shows promising chemoprotective properties against cisplatin-induced side effects. We are also evaluating the chemoprotective effect of UTL-5g against oxaliplatin – as it is more widely prescribed nowadays – with the support of a newly-issued Small Business Innovation Research (SBIR) Phase I grant. The other application is its radioprotective effect. Under a Phase I Contract of the SBIR programme, we showed that UTL-5g could protect an irradiated lung by lowering the elevated levels of TNF-α and TGF-β. This is another promising area we may pursue.

Do you have any results from the SBIR Phase II study that you can discuss?

In addition to further confirming that UTL-5g reduces the side effects induced by cisplatin, we have investigated the metabolic behaviour of UTL-5g, ultimately finding that it is dramatically different from a structurally similar drug, leflunomide. I believe this difference is one of the main reasons that UTL-5g has a lower acute toxicity than leflunomide. This was a significant finding and it formed the basis of a published review paper. Another important finding originated from the repeat dose toxicity study, in which we treated mice with up to 1,500 mg/kg per day orally for seven days; there were no treatment-related deaths and only minimal, non-limiting toxicological effects on clinical signs and clinical pathology endpoints. Histopathology revealed that the spleen was a target organ. Microscopically, increased haematopoiesis of the spleen was seen in all UTL-5g treatment groups, which is consistent with the platelet protection effect of UTL-5g.

You have been working on your current project since 2009 and it is due for completion this summer. What is the next step after SBIR Phase II?

We'll carefully review the overall data and decide whether it makes sense to add more studies and file an investigational new drug application for chemoprotection. We may also consider the possibility of using it as a radioprotector. Furthermore, we now have new compounds – based on the UTL-5 platform – in the pipeline under preclinical development. If the new compounds are significantly better than UTL-5g, we may have a tough decision as to what to do next.

Protection perfection

Researchers at US drug discovery company **21st Century Therapeutics, Inc.** may hold the key to advancing chemoprotection, potentially enabling clinicians to negate the side effects of chemotherapy

MEDICAL SCIENCE HAS already seen a number of breakthroughs in the field of cancer treatment, and pre-eminent among these has been the discovery of the platinum-based anti-cancer drugs. The first of its kind, cisplatin, was approved by the Food and Drug Administration (FDA) for clinical use in the US in 1978 – and its efficacy is such that it remains a popular component in combination chemotherapies today. At the time, its discovery revolutionised the treatment of this persistent and multifarious disease. Although particularly effective against testicular cancer, its introduction saw cure rates for most other forms of cancer improve significantly.

There was, however, a price to be paid for cisplatin's success – and more than 30 years later, the physical cost of effective chemotherapy still lingers on in patients receiving treatment. The platinum-based chemotherapeutic agents target rapidly dividing cells, curbing tumour growth but also leading to hair loss and damage to the skin and nails. Cisplatin adds fresh toxicities of its own. With repeated doses, damage to the kidney cells evolves slowly but predictably, and in 25-30 per cent of cases the drug will affect the bone marrow as well, reducing the production of platelets and white blood cells. Finally, and most importantly, hepatotoxicity is induced in high doses, limiting the amount of cisplatin that can be used at any given time.

CHEMOPROTECTION

The side effects of chemotherapy, and platinum-based chemotherapy in particular, limit an otherwise very effective treatment. Much attention has therefore been devoted to the development of chemoprotective agents to nullify them. As it stands, the US Food and Drug Administration (FDA) has approved only one adjuvant to cisplatin for this purpose: amifostine, marketed under the trade name Ethyol. The use of this drug is becoming increasingly widespread, but when used in conjunction with cisplatin it remains controversial. The main problem is that the two substances are not pharmacologically compatible, causing thyol to have a tumour-protective effect.

Ethyol is also associated with side effects of its own – including dizziness, nausea, vomiting, hypotension and, in some cases, cutaneous reactions – as well as being relatively inconvenient to administer (by intravenous infusion). A novel chemoprotector for use with cisplatin would therefore be an extremely useful clinical tool, and the development of such an agent is the current goal of Dr JiaJiu Shaw's research group at 21st Century Therapeutics, Inc., a small drug discovery company based in Michigan, USA. Their efforts have focused on the tumour necrosis factor alpha (TNF-α) modulator UTL-5g. This drug candidate, selected from their own small-molecule library, has already brought forth some promising results.

LEAVING THE COMPETITION BEHIND

Having secured funding from the National Institutes of Health (NIH) for a Small Business Innovation Research (SBIR) Phase I trial of UTL-5g, Shaw and his collaborators had the opportunity to investigate the potential of their candidate against Ethyol. UTL-5g was the ideal subject for further testing because it is a

NOVEL SMALL-MOLECULE TNF-α MODULATORS AS CHEMOPROTECTIVE AGENTS

OBJECTIVES

Short term objective: to design and identify a promising radioprotective/chemoprotective agent that is significantly better than the currently available.

Long term objective: to develop a novel drug for chemoprotection/radioprotection to reduce the suffering of patients and increase the chemotherapy/radiotherapy outcome.

KEY COLLABORATORS

Dr Frederick Valeriote, researcher in cancer and radiotherapy

Dr Ben Chen, researcher in haematology and immunology

FUNDING

Funded by the National Cancer Institute (NCI), National Institutes of Health (NIH)

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JIAJIU SHAW received a PhD in Chemistry from the University of Kansas and completed his postdoctoral work in Organometallic Chemistry at the University of North Carolina. He has worked in the pharmaceutical industry for over 25 years with extensive experience in the fields synthetic chemistry, pharmacokinetics, formulation, quality control and preclinical development. Shaw is currently President of 21st Century Therapeutics, Inc. He is the principal investigator for a number of NIH-funded research grants related to immune-mediated diseases and cancer. Shaw's recent research efforts are in chemoprotection and radioprotection.

patented TNF-α modulator functional *in vivo*, and is easily synthesisable via a simple one-batch, two-step reaction from readily available starting materials. The SBIR Phase I trial involved numerous animal studies, and the findings were overwhelmingly positive.

In rodent models, UTL-5g lowered elevated levels of several substances associated with increased toxicity following cisplatin treatment; blood urea nitrogen, creatinine, blood aspartate transaminase and alanine transaminase levels, elevated by cisplatin, all fell significantly following UTL-5g treatment, constituting a chemoprotective effect. What is more, the agent achieved the same extent of protection as amifostine at a greatly reduced dosage; 60 mg/kg of UTL-5g was equivalent to 200 mg/kg of amifostine. It not only avoided the apparent tumour-protective effect, but actually added positive effects: Shaw's researchers observed and increased platelet count, and a dose-dependent reduction in blood TNF-α.

The acute toxicity to mice was also low, with the median lethal dose shown to be greater than 2,000 mg/kg, compared with Ethyol, which has a median lethal dose of just 320 mg/kg. Perhaps most surprising of all, however, was the finding that, rather than reducing the efficacy of cisplatin (as Ethyol does) UTL-5g actually enhanced the anti-cancer effect of the chemotherapeutic agent in one animal study. This impact is unprecedented and confounds conventional wisdom on the subject; the increase in platelet count, likewise, demonstrates a significant protective effect that has not been seen alongside potent kidney and liver protection in any other agent so far. Based on these results, UTL-5g indeed appears to far exceed Ethyol in efficacy and utility – and represents an attractive group of therapeutic agents for further study.

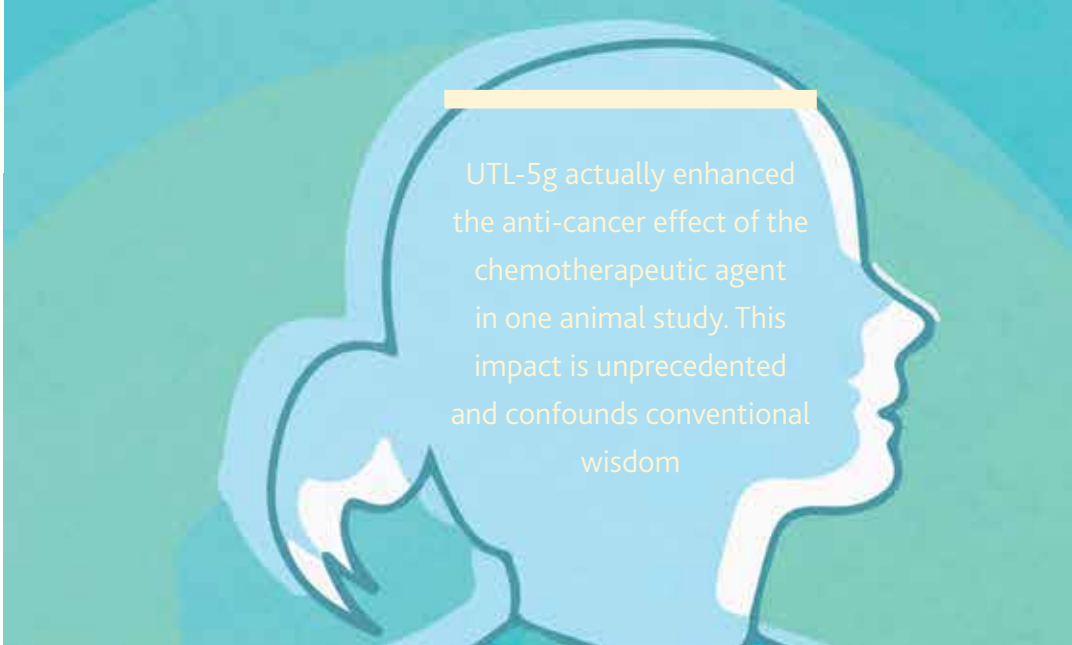
THE UTILITY OF UTL

In the summer of 2011, the team had the opportunity to conduct this study further when they received US $1.1 million from the NIH – their Phase II SBIR grant. As part of this new phase of study, the group obtained further proof of UTL-5g's chemoprotective effects, as well as examining the mechanisms by which it achieves these effects *in vivo*, and its pharmacokinetic properties. A more precise and detailed investigation of the substance's toxicity has also been carried out. With positive results, measures to develop the formulation and upscale production of the active pharmacological ingredients are also planned. Based on the success of this work, 21st Century Therapeutics, Inc. has been able to form a number of productive partnerships in the intervening years, and has secured various grants to develop UTL-5g in new directions in addition to pursuing its continuing preclinical development.

Currently, Shaw and his collaborators are examining the possibility of using UTL-5g as a radioprotective agent. Early studies demonstrated the substance could mitigate the side effects of radiotherapy *in vivo* much as it did with chemotherapy, and the Michigan scientists have now shown that UTL-5b and -5d also have similar effects. At the same time, they are also exploring the effect of UTL-5g in combination with other platinum-based chemotherapeutic agents, beginning with oxaplatin. With better platelet protection, there is hope that this can help make the more widely-prescribed agent more effective.

SMALL BUT SUCCESSFUL

Now the recipient of four separate SBIR grants for its work with UTL-5g, it is clear that 21st Century Therapeutics, Inc. is a small company that packs a big punch – and with ongoing collaborations on an international scale, as well as a history of work with institutions like National Cancer Institute, it is well placed to succeed. As for UTL-5g, the road from bench to bedside is known to be a long one, but this is a protective agent that shows distinct and surprising potential both in the context of chemo- and radiotherapy. It is the solution clinicians and patients are crying out for.



21st Century Therapeutics