A formulation approach to prevent bladder cancer

Drs Helen M Burt, Clement Mugabe, Michael Parr and Richard Liggins are working together to exploit the potential of nanotechnology in preventing the progression of bladder cancer. They discuss their promising discoveries and explain how they surmounted challenges along the way.

Can you begin by introducing yourselves and your respective roles within your collaborative research?

HB: I am Professor in the Faculty of Pharmaceutical Sciences and the Associate Vice President, Research and International, at the University of British Columbia (UBC), Canada, and one of the co-founders of The Centre for Drug Research and Development (CDRD). My expertise lies in developing polymer-based drug delivery systems, and I led the interdisciplinary research team that developed and characterised the novel, docetaxel-formulated, hyperbranched polyglycerol (HPG) nanoparticulate formulation for intravesical delivery in bladder cancer.

CM: I am Associate Scientist in the Drug Delivery Division at CDRD with expertise in the formulation and characterisation of polymeric and lipid-based nanoparticulate drug delivery systems. I completed my PhD in the Faculty of Pharmaceutical Sciences at UBC under the supervision of Helen, where I was involved in the development of the HPG-docetaxel formulations for application in bladder cancer therapy.

MP: I am President and Chief Scientific Officer of Sitka Biopharma, a company that I founded as a result of my role as Director of Commercial Project Development within CDRD’s commercial arm, CDRD Ventures Inc., recognising the value that this technology represented toward vastly improved therapy for bladder cancer. As well as coordinating several operations within the company, I am also responsible for promoting the rapid clinical development of this very promising technology.

RL: I am Head of Analytical Chemistry at CDRD and Adjunct Professor in Pharmaceutical Sciences at UBC. I have expertise in polymeric drug delivery and am responsible for several product development programmes at CDRD, including development of the HPG platform with its lead indication in bladder cancer. I also lead a group of CDRD scientists involved in a collaborative relationship with the University and who work very closely with Sitka and other UBC labs.

Your research is concerned with finding a more effective means to treat bladder cancer. How prevalent is this cancer worldwide and what are the drawbacks of current therapies?

ALL: Bladder cancer is the ninth most common cancer. The drawbacks of current intravesical chemotherapies (IVC) are poor uptake and short residence time in the bladder. Conventional IVC, such as mitomycin C, are typically maintained in the bladder for a short period of time. Novel approaches are therefore needed to prolong drug residence time and promote uptake into bladder tissues.

Can you explain what HPGs are in lay terms?

ALL: HPGs are small, spherical, highly branched and single molecules, also termed ‘unimolecular micelles’, with a core that repels water and shell that attracts it, connected by strong chemical bonds. HPGs are structurally distinct from other nanoparticulate delivery vehicles such as micelles and liposomes and are much smaller in size (5-15 nanometres).

Your investigations utilised docetaxel formulated in mucoadhesive nanoparticles. What were the results?

ALL: Efficacy studies in mouse bladder orthotopic tumour models have shown that the docetaxel-formulated mucoadhesive HPGs produce promising antitumour efficacy and significantly outperform Taxotere, the commercially available docetaxel formulation.

Our lead programme, STK-01, is HPG-docetaxel for the intravesical treatment of non-muscle invasive bladder cancer. Validated preclinical proof-of-concept pharmacokinetic and pharmacodynamic studies in mice have demonstrated significantly greater drug concentrations, residency times and tissue penetration, leading to a marked reduction in tumour growth when compared to conventional docetaxel. These models also showed significant shrinkage of much larger established bladder tumours.

Are there any particular challenges you have faced in bringing this technology from the lab to the marketplace?

ALL: One of the most challenging aspects has been overcoming the financial ‘valley of death’ development gaps between the discovery stage and the interests of various funding partners. For example, the technology’s viability at an early stage depended in large part on its safety profile. While granting agencies funded the discovery and proof-of-concept stages, finding ways to answer the most critical development questions is always a challenge.

How did you overcome them?

ALL: The key for our group was access to the drug development capabilities of CDRD, who provided a strong multidisciplinary team, with the ability to seek support for the technology from both the academic and industry sectors. These stakeholders collectively understand the value of innovation, proven science and data to address the practical concerns of drug development.
BLADDER CANCER IS the ninth most common cancer in the world and is notoriously difficult to treat effectively. Indeed, it is the most expensive form of cancer to treat on a per-patient lifetime basis. This is due to the costly surveillance and multiple cycles of treatment required to manage the high rates of both recurrence and progression.

In the US, there are approximately 70,000 new cases of bladder cancer per year, with an estimated 75 per cent of these patients presenting with non-muscle invasive bladder cancer (NMIBC). Following diagnosis, there is a range of possible treatment procedures, and the chosen course of action is largely dependent on which form the cancer has taken and on the individual’s general health. For those NMIBC patients in a higher risk category, for instance, the current most effective intravesical immunotherapy for reducing the risk of progression is Bacillus Calmette-Guerin (BCG). However, for patients in a lower category, BCG is generally not used as it is poorly tolerated and carries a risk of systemic infection.

POOR PERFORMANCE

Patients with NMIBC require continuous monitoring and repeated surgical procedures, known as transurethral resection of a bladder tumour (TURBT). However, an estimated six out of 10 NMIBC patients’ tumours return despite undergoing TURBT, of which about 30 per cent progress to more aggressive forms of the disease.

These poor outcomes are primarily the result of inadequate adjunctive chemotherapy delivery options. It is recommended that patients undergoing TURBT should simultaneously receive intravesical chemotherapy (IVC) – that is, the administration of liquid drugs into the bladder through a catheter – to kill residual elements of the tumour or prevent its recurrence. Yet current IVC regimens provide only a 10-15 per cent reduction in recurrence rates and have completely failed to prevent the cancer’s progression in higher-grade patients.

There are several reasons for the disappointing performance of IVC. First, the urothelium is highly impermeable, which makes absorption of the local chemotherapeutics used extremely difficult. Second, effective exposure to the drugs is limited as they are rapidly washed out when the patient urinates – an action that typically occurs within two hours of the commencement of the treatment procedure. In addition, the pH levels of urine and the dilution of the drugs through urine production further interferes with the effectiveness of IVC.

Remarkably, less than 1 per cent of the drug instilled into the bladder is distributed into its intended destination – the bladder wall. If drug delivery could be improved, and the absorption of local chemotherapies could be significantly enhanced, it is likely that IVC would prove a far more effective means of reducing both the recurrence and progression of NMIBC into a more aggressive form.

NANOPARTICULATE PLATFORM TECHNOLOGY

In response, researchers at The Centre for Drug Research and Development (CDRD) – Canada’s national drug development and...
The researchers have developed nanoparticulate drug delivery platform technology that dramatically improves the efficacy of existing standard treatment procedures for non-muscle invasive bladder cancer. commercialisation centre – along with urologists from the Vancouver Prostate Centre, have spent the past few years attempting to overcome the limitations of current bladder cancer treatments. Through innovative research, their end goal has been preventing the recurrence and progression of NMIBC. By developing a better treatment that targets the disease in its earlier stages, they intend to offset the need for highly invasive treatments further down the line, consequently saving lives and reducing the economic burden of bladder cancer.

Led by Professor Helen M Burt, a scientist at the University of British Columbia and one of the founders of CDRD, the researchers have developed nanoparticulate drug delivery platform technology that dramatically improves the efficacy of existing standard treatment procedures for NMIBC. Following preclinical proof-of-concept, the technology has since been transferred to a spin-out company entitled Sitka Biopharma.

The technology in question combines a nanoparticulate drug delivery platform based on hyperbranched polyglycerols (HPGs) with docetaxel, in a single formulation specifically designed for intravesical administration into the bladder. Intriguingly, docetaxel is highly active against a wide variety of systemic cancers and is used clinically in metastatic bladder cancers – yet to date it has not been approved for IVC. As an antimiotic chemotherapy medication, docetaxel is

COMMERCIAL DEVELOPMENTS

As a result of four years of successful incubation and collaboration between Burt and the other researchers, the commercialisation vehicle of The Centre for Drug Research and Development – CDRD Ventures Inc. – announced the launch of a new spin-off company in December 2013. Entitled Sitka Biopharma Inc., this company is focused on driving the clinical development of hyperbranched polyglycerols (HPG)-docetaxel for the intravesical treatment of non-muscle invasive bladder cancer (NMIBC). It is anticipated that this will become a leading product in a market that has been highly underserved to date, replacing the use of intravesical chemotherapies that are currently used in both low-grade and more advanced disease states prior to bladder removal.

Indeed, evidence of reduced recurrence rates and inhibited disease progression will lead to significant alterations in current treatment protocols and guidelines for bladder cancer, dramatically changing the existing market for intravesical chemotherapy.

Sitka is also planning to use the core technology platform as a foundation for developing additional applications where ineffective delivery across the tissue surface hampers local drug delivery. “Here, one area will be to expand the existing product into additional surface malignancies where the general treatment paradigm is similar to NMIBC – stage 3 ovarian cancer, for example,” Burt describes. “The second area will be to develop the technology for additional drug classes and clinical applications.”
A MUCOADHESIVE HPG FORMULATION

Hyperbranched polyglycerols (HPGs) are composed of one small, nondegradable polymer molecule, which means they retain their structure even when diluted. Conjugating amine groups onto the outer shell of the HPGs enables strong adhesion to urothelial mucin chains in the bladder, as well as extensive cellular binding and uptake. Formulating these mucoadhesive nanoparticles with docetaxel increases the body’s exposure to the drug, demonstrates antitumour efficacy and, perhaps most importantly, appears to be well-tolerated in the bladder.

Yet Burt and her collaborators overcame this challenge through developing an HPG formulation of docetaxel. Importantly, the hydrophobic core of the polymer increases the solubility of the drug, while its outer elements are hydrophilic, in turn enabling hydration and solubility in urine. This boosts the suitability and efficacy of the use of HPG-docetaxel in IVC and allows the hydrophobic docetaxel to partition into the bladder wall.

INCREASED EXPOSURE

Impressively, the specialised features of Burt’s nanotechnology platform result in both the modulation of tight junctions and improved urothelial permeability. Not only does this enhance drug delivery by enabling it to penetrate tissue when it comes into contact with the urothelium, but it also dramatically increases the residency time of the drugs within the bladder. This in turn raises patient exposure to the drugs, accordingly strengthening the effectiveness of the treatment.

In order to increase contact with the urothelium, the exterior of the HPG molecule contains amines that enable adhesion to the bladder’s surface. These mucoadhesive polymers join to the mucin gel layers covering the mucosal membranes, paving the way for the targeting of mucin glycoproteins on the surface of the urothelium.

PROMISING PATHWAYS

At present, the most immediate benefit of the research conducted by Burt and her collaborators is the HPG polymer’s potential for increasing drug uptake in other tissues where there are problems associated with conventional delivery. Beyond this, the research has many more far-reaching implications. Indeed, the development of the HPG polymer represents a platform technology that, through variations to its chemistry and combinations with different drugs, could result in a wide range of different uses. "Over the next 10 years, based on the initial success in treating bladder cancer with this approach, we are planning to explore and exploit the other potential uses of this polymer," explains Burt. "To this end, our team is currently evaluating many other early-stage ideas for using the polymer as both a biomaterials and a therapeutics agent.”

By developing and expanding upon existing technology, Burt and her team have forged a path that could lead to extremely positive consequences, not just for the treatment of bladder cancer but the treatment of other cancers and potentially even other diseases.