Nanomaterials in drug delivery systems

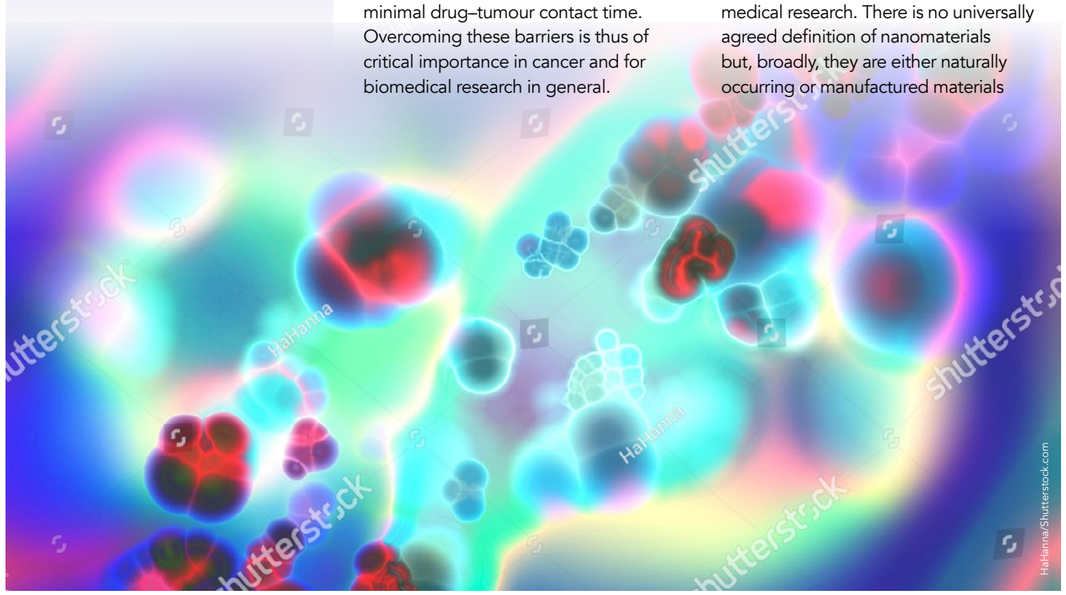
The inability of many treatments to reach the intended target and release their therapeutic effects is a major challenge for cancer research. There is an unmet need for improved drug-delivery systems which reduce off-target effects. Dr Benedict Law, Dr Vanessa Bellat and colleagues at the Weill Medical College of Cornell University, New York, USA, develop complex novel drug-carrier systems using nanomaterials. Specially designed to overcome barriers within living tissue, the aim is to maximise the therapeutic effect of oncology drugs for some of the deadliest cancers.

In cancer research, the goal is not only to develop highly effective therapies but to ensure that these drugs are taken up by the intended tumour targets; any non-specific uptake by tissues and organs (off-target effects) are limited. A treatment could demonstrate excellent results in laboratory studies but if it can't reach and penetrate the target and, in some cases, sustain drug release, it will not be effective. A drug-delivery system should be able to escape immediate discharge by the body's clearance system, the reticuloendothelial system (RES), and stimulate its uptake by tumours. Tumour cell membranes are inherently leaky, which aids penetration and drug delivery to the target cell. However, only 0.7% of administered therapeutic drugs reach solid tumours because the drug can be removed by organs, absorbed within the blood system, and excreted, resulting in minimal drug–tumour contact time. Overcoming these barriers is thus of critical importance in cancer and for biomedical research in general.

Dr Benedict Law, Dr Vanessa Bellat, and colleagues at the Weill Medical College of Cornell University, New York, USA, focus on this important aspect by designing and developing new drug-carrier systems for potential use in diseases such as triple-negative breast cancer tumours (TNBC), diffuse intrinsic pontine glioma (DIPG), and nonmuscle invasive bladder cancer (NMIBC). Their preclinical research studies in animals show promising results, unlocking possibilities for much-needed improvement in therapy efficacy for cancer patients in the future.

NANOMEDICINE

Nanomedicine is the use of nanomaterials and nanotechnology in the field of medicine to aid diagnosis, monitoring, and treatment of disease. It is an exciting and rapidly growing field offering immense potential in medical research. There is no universally agreed definition of nanomaterials but, broadly, they are either naturally occurring or manufactured materials that have structures in the range of one to 100 nanometers. In the human body, natural cellular entities such as proteins, enzymes, lipids, and peptides, among others are considered to be nanostructures. Nanocarriers are drug-delivery vehicles designed to improve drug-delivery specificity and reduce off-target effects in the body. Their design flexibility enables nanocarriers to be modified in shape, size, or magnetic field, and are joined with molecules to increase uptake and penetration into tumour cells. Such carriers ultimately determine the pharmacokinetics of the drug (the activity of drugs in the body over a period of time), as they are designed to aid specific uptake by target cells.



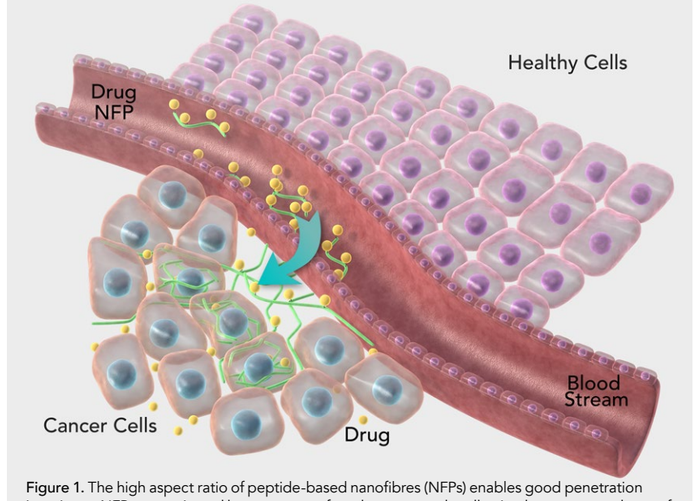


Figure 1. The high aspect ratio of peptide-based nanofibres (NFPs) enables good penetration into tissue. NFPs are activated by enzymes to form large networks, allowing longer-term release of the therapeutics they carry.

Increasingly, peptide-based nanofibres (NFPs) are being explored for their use in a range of biomedical applications including drug delivery because of their size, properties, design flexibility, and capacity for customisation. Their structure has a high aspect ratio, enabling better penetration into tissue. Within tumour cells and in cellular interstitial spaces (the space surrounding cells), NFPs are activated by enzymes and can form large networks enabling longer-term release of the therapeutics they carry (Figure 1). Research has explored the use of NFPs to aid delivery of drugs in diseases such as cancer, myocardial infarction, and fracture healing, among others. Law and Bellat have developed novel NFP systems that incorporate drug molecules and imaging agents – assisting their uptake by tumours and their ability to be monitored. These innovative systems have been described in a number of key studies by the Cornell University researchers.

DRUG-DELIVERY SYSTEMS IN BREAST CANCER

In the journal *Biomacromolecules*, Law and Bellat first reported their design of two nano transformers: NTF1 and NTF2 as carriers of mertansine (DM1), a microtubule inhibitor drug used in breast cancer. Their study in human TNBC cells demonstrated that enzymes such as cathepsin B (often upregulated in cancer cells) can induce structural changes in NTF1 and NTF2, causing release of the drugs they are carrying. Of interest, cathepsin B induces different releases (a fast release in NTF1) compared to induction of large networks, storage reservoirs, and delayed release in NTF2. In TNBC, NTF1 showed superior cytotoxic (cell-killing) ability compared to the antibody-drug conjugate (T-DMI) and similar cytotoxic activity to free DM1. Law and Bellat suggest the properties and drug-release profile of NTF1 make it a potential carrier for other drugs and this therapeutic potential requires further investigation.

In another study, the researchers investigated a biocompatible glutathione (GSH)-NFP delivery system in animals with TNBC tumours. This system has customisations for specific shape and charge to enhance tumour delivery, and can be activated by enzymes to control drug release and retention. Results revealed reduced retention by the RES, and formation of larger networks in the tumour enabling slower drug release and retention of the drug for weeks. Overall, it had better targeting and penetration of the tumour than NFP without GSH and was associated with improved survival of mice with TNBC tumours.

Nanomedicine is an exciting and rapidly growing field offering immense potential in medical research.

APPROACHES IN DIFFUSE INTRINSIC PONTINE GLIOMAS

Diffuse intrinsic pontine glioma (DIPG) is an inoperable brain tumour. It is the most prevalent type of paediatric brainstem glioma, has poor prognosis and a short life expectancy of approximately one year after diagnosis. Onset is typically between the age of five to ten years. In addition to being inoperable, drug delivery to the brain to treat the tumour is compounded by the blood–brain barrier (BBB) and thus sub-optimal drug concentrations reach the brain. Convection-enhanced delivery (CED) can deliver drugs to the target area via a catheter to reduce systemic effects. This can circumvent the BBB but unfortunately after CED administration, there is rapid drug clearance, which reduces therapeutic effects. To compensate for this rapid clearance, multiple longer infusions may be performed but this carries clinical risk. Improvements in both drug delivery and drug efficacy are therefore urgently needed.

Law and Bellat studied human DIPG cells and demonstrated the cytotoxicity of NFP-DM1. In mice, DM1 conjugated to

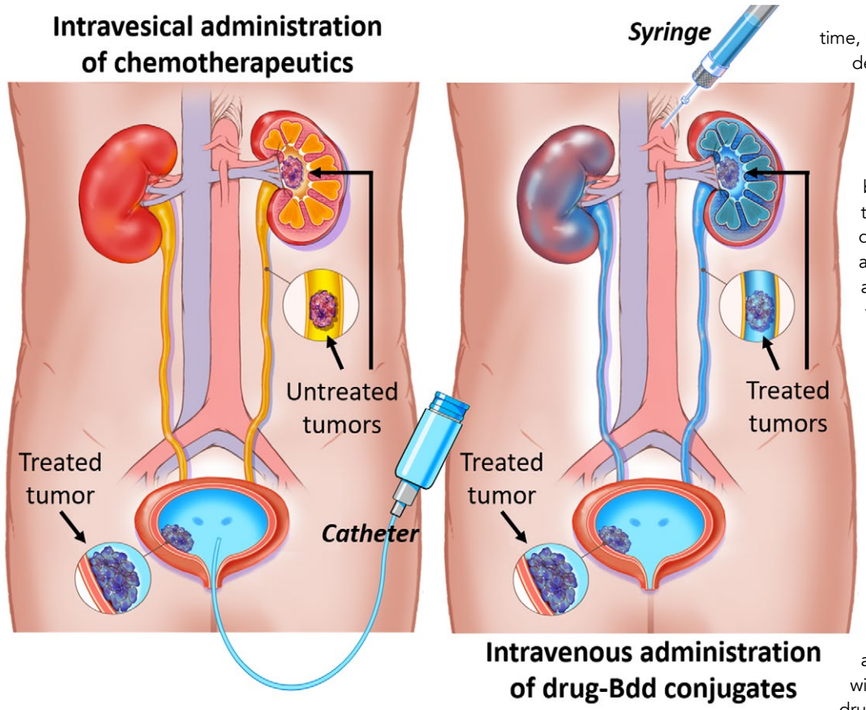


Figure 2. The new systemic approach developed by Law and Bellat will improve the treatment outcomes of bladder cancer by covering the entire urinary system, prolonging tumour–drug exposure. From Bellat et al *Cancer Res* 2022 doi.org/10.1158/0008-5472.CAN-21-2897

Law and Bellat develop complex customised approaches which enhance drug delivery and reduce off-target effects.

NFP given via CED successfully bypassed the BBB. It was taken up by tumour cells and demonstrated a long drug retention at the local site with a clearance half-life of 60 days. The CED NFP-DM1 delivery approach reduced disease progression and doubled survival rates compared to mice treated with free DM1. Due to its local delivery, the research team suggest this innovative approach could reduce systemic drug toxic burden as well as reducing risks associated with multiple prolonged infusions required to compensate for rapid drug clearance.

More research is required; however, these novel findings are a major breakthrough, and such a clinically translatable approach has the potential to improve survival for patients with DIPG. Furthermore, it brings into question whether drug candidates previously stopped because of poor solubility and delivery properties could be reinvestigated for their efficacy because of the ability of CED-delivered NFP conjugates to effectively target the tumour.

URINARY DRUG-DISPOSING APPROACH IN NMIBC

Non-muscle invasive bladder cancers have a high rate of reoccurrence, require constant monitoring and bear a significant healthcare financial cost. Standard treatment (intra-vesical therapy or IT) administers drugs to the bladder via a catheter. This invasive procedure has side effects and risks, and limited drug–tumour contact time. Also, IT is unable to effectively deliver therapy to the ureter and renal pelvis areas of the urinary system.

To address the unmet need for more efficient non-invasive delivery systems that enable longer drug–tumour contact time, Law and Bellat have developed a urinary drug-disposing (UDD) approach to treat NMIBC (Figure 2). Their approach uses a bio-inert peptide (Bdd) to carry the cancer drug DM1 to the target area. This design takes advantage of the fact that peptides are exclusively and rapidly cleared by the renal system, enabling specific delivery to this area.

This UDD approach was administered non-invasively to mice with human bladder tumours. Non-invasive intravenous administration enables wider coverage of the drug to all parts of the urinary system including the ureter and renal pelvis which current therapies do not allow. Superior efficacy in controlling tumour growth and prolonged survival of mice was found with this approach compared to the drug mitomycin (used in intra-vesical therapy).

The study also explored the UDD approach in renal carcinomas and demonstrated improved survival and complete elimination of the tumour in half of the mice. The researchers suggest another potential application for the UDD is in treating kidney and bladder infections where the Bdd could be conjugated to antibiotics and this avenue warrants further research.

Overall, this vital area of research emphasises the utility and potential of nanocarriers in drug-delivery systems. Law and Bellat develop complex customised approaches which enhance drug delivery and reduce off-target effects, and have demonstrated improved therapeutic efficacy in preclinical research. Such findings provide the platform for further studies of these novel systems in a number of diseases and offer hope for more targeted effective treatment in the future.

Behind the Research

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Research Objectives

Law and Bellat develop nanomaterials and other novel drug-delivery systems to improve patient outcomes for a range of diseases.

Detail

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Bio

Dr Benedict Law completed his PhD at the University of Manchester (UK). He is currently an associate professor at the Molecular Imaging Innovations Institute, Department of Radiology, Weill Cornell Medicine. His research focuses on designing novel delivery systems for therapeutic applications. He also applies multimodal imaging techniques to study the pharmacokinetic and biodistribution of anti-cancer treatments.

Dr Vanessa Bellat trained as a nanotechnology scientist and received her PhD from the University of Burgundy (France). She joined the Molecular Imaging Innovations Institute in the department of radiology at Weill Cornell Medicine first as a postdoctoral associate, and now pursues her academic career as Instructor of Chemistry. Her main objective is to design smart nanomedicines displaying organ-specific affinity and targeting properties to achieve more effective chemotherapeutic treatments.

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- Department of Defense, US
- National Cancer Institute, US

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Personal Response

What are the next steps for taking these drug-delivery systems forward, both in preclinical research and beyond?

"Drug delivery is only the first step for a successful treatment. Tumours are diverse, both endemically (intra and inter-tumoral) and physiologically (genomic and phenotypic), in nature. They also interact with the surrounding ecosystem (environment) and escape from immune system to favour disease progression. With their unique tumoral accumulation, penetration, and retention properties, we can potentially apply our delivery systems to targeted immunotherapy. Other nanocarriers can also be designed to highjack the tumour microenvironment and restore the immune system against cancer cells. In combination, new imaging approaches can be applied to interrogate immune surveillance."

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