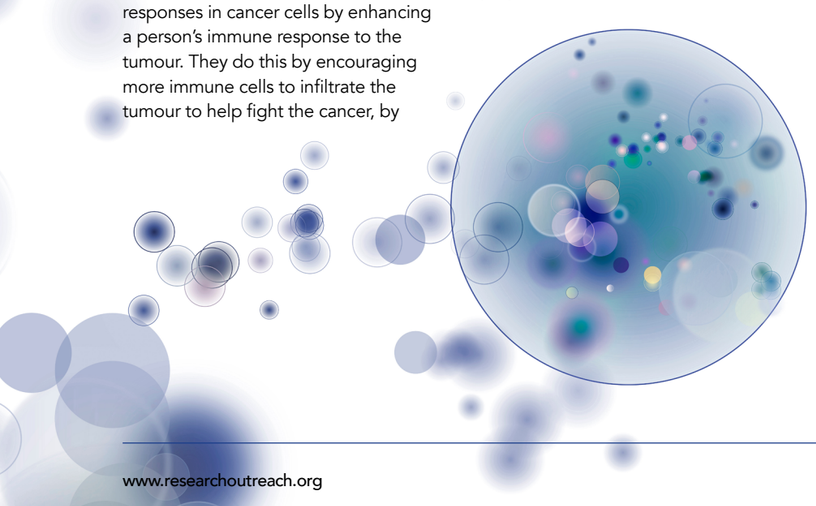
Nanoparticles as Trojan horses

A safe and effective way to deliver oncolytic viruses to treat all cancers

Advanced cancer often comes with a lack of treatment options. Immunotherapies like cancer-killing viruses – oncolytic viruses (OVs) – are becoming increasingly popular but are currently limited by their inability to be administered into the blood. However, Dr Faith Howard and Dr Munitta Muthana, researchers at the University of Sheffield in the UK, demonstrate that OVs can be injected into the bloodstream with nanoparticles. They show that OV delivery with nanoparticles is a safe treatment option and highly effective at combating cancer that spreads to other parts of the body.

Cancer is becoming increasingly harder to treat, with more patients now resistant to chemotherapies. There is also a need for more treatment options for patients with advanced diseases. Cancer-killing oncolytic viruses (OVs) provide an exciting new treatment modality to explore, revolutionising how we treat cancer. OVs represent a small part of a new era of therapeutics in cancer, called immunotherapies. This treatment utilises and enhances the person's immune system to fight cancer. OVs are highly effective towards rapidly dividing cancer cells as they can selectively infect and destroy cancer cells by self-replicating and multiplying inside them. OVs also promote anti-tumour responses in cancer cells by enhancing a person's immune response to the tumour. They do this by encouraging more immune cells to infiltrate the tumour to help fight the cancer, by creating what is known as a 'hot tumour'. This infiltration is essential as some cancers are immunologically 'cold' and, hence, hard to treat.

Currently, three OV treatments are approved for melanoma, metastatic melanoma, and head and neck tumours – they are called Regvir, Oncorine, and T-Vec, respectively. The most common delivery method for these OV therapies is to inject the tumour directly by intratumoural delivery (IT), as it ensures that the OV therapy reaches the tumour at a high concentration and is less likely to cause unwanted side effects. Although IT delivery displays a safe profile paired with promising anticancer properties, unfortunately, it is only suited to superficial tumours close to the skin's surface, like melanoma. IT delivery of OVs has had less efficacious clinical response rates for inaccessible or widely distributed tumours.



Dr Faith Howard, a postdoctoral researcher at the University of Sheffield, UK, and her colleague Dr Munitta Muthana are looking to broaden the use of OV treatment in more advanced cancers using technology in nanomedicine called nanoparticles. Nanoparticles provide a protection and delivery mechanism for OVs to access hard-to-reach tumours and cancers that have spread (metastatic). Howard hopes to pave the way for OV therapy to be used with nanoparticles so that all cancers can be treated with OV therapy.

BENEFITS OF NANOMEDICINE

Nanomedicine is a growing field in pharmaceuticals and cancer therapeutics that combines technology and medicine to aid the diagnosis and treatment of disease. Since 1995, over 50 nanoparticles for clinical use have been approved by the US Food and Drug Administration (FDA). Nanoparticles are small carrier vehicles that vary in shape, size, and function with an average diameter of 200nm (nanometres). This size is perfect for squeezing through tiny blood vessels called capillaries to reach all body parts. Their use is becoming increasingly popular, especially for the delivery of chemotherapy drugs, due to their ability to transport hydrophobic drugs (drugs that repel water). This feature is important as around 75% of anticancer drugs are hydrophobic, which can affect the drug's absorption and effectiveness. Nanoparticles are often a favourable option to limit off-target effects and deliver the drug to only the target site.

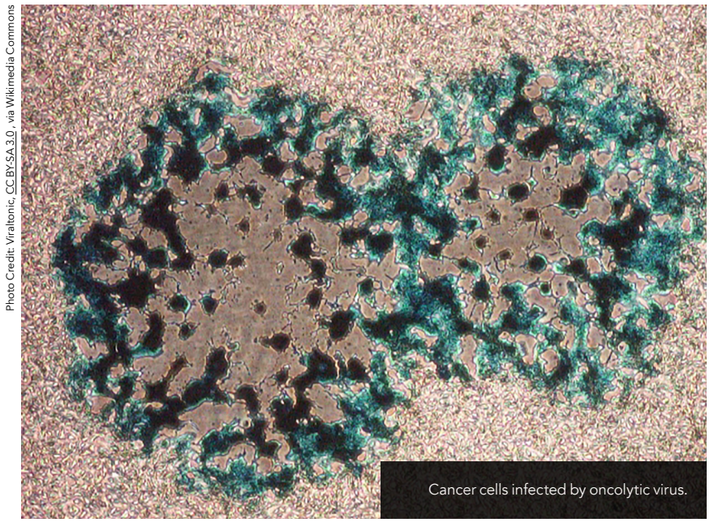


Photo Credit: Viraltonic, CC BY-SA 3.0 , via Wikimedia Commons

Cancer cells infected by oncolytic virus.

Muthana and Howard have demonstrated that an intravenously administered OV can enhance tumour targeting, reduce tumour growth, and improve survival of a mouse model by 50%.

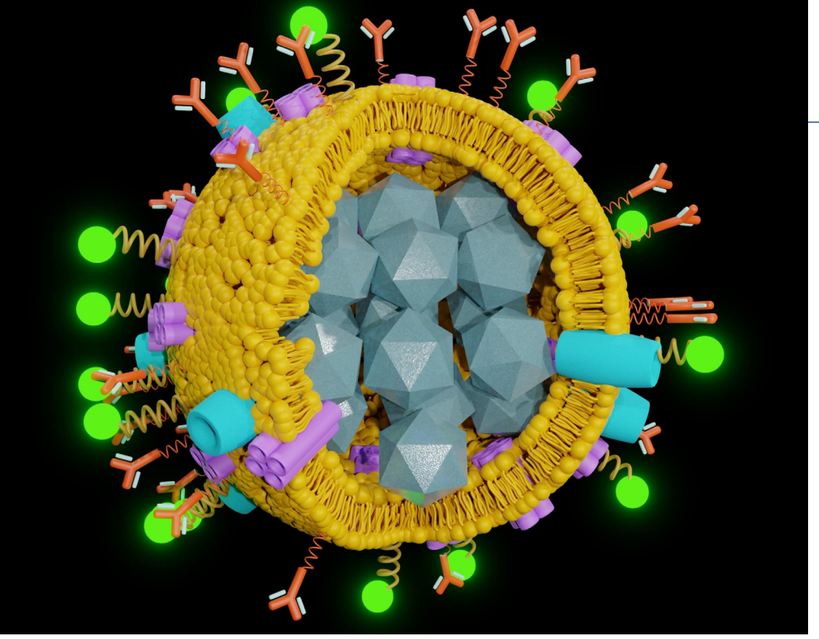
Howard states that carrier systems like nanoparticles are not new to cancer treatment, with many cancer therapeutics like small molecule inhibitors utilising their benefits. Some of these benefits include increased solubility and cell uptake as well as extended time in the circulation without causing any unwanted, toxic side effects. However, the delivery of OVs to the tumour following administration to the bloodstream requires navigation and a method to prevent early clearance by the body's immune system. Some nanoparticle designs like liposomes, dendrimers, and polymeric nanoparticles show cell-recognition and binding advantages and shielding. Further developments include magnetic steering which provides active guidance and controlled release where nanoparticle cargo is only released at the target via environmental stimulus.

NANOPARTICLES IN ACTION

Muthana and Howard have demonstrated that an intravenously administered OV can enhance tumour targeting, reduce tumour growth, and improve survival of a mouse model by 50%. A genetically modified variant of herpes simplex virus-1 (HSV-1) was paired with nanomagnets that were isolated from specialised bacteria. A nanomagnet is a type of nanoparticle that can be directed using magnetic fields. These 'magnetotactic' bacteria have magnetic crystals inside of them that respond to magnetic force. Magnetic targeting was used in these experiments to drive the magnet-coated OV to the tumour site. These experiments with HSV-1 induced the shrinking of primary breast cancer in a mouse model and prevented the development of further metastasis. This treatment strategy increased survival in the mouse model by 50%. No adverse effects were found.

In addition, Muthana and Howard have shown that it's possible to also use

Tumour microenvironment, including immune cells and fibroblasts.



The team encapsulated an oncolytic virus into a liposome layer so that it wouldn't be neutralised by immune cells before it reached its target.

OV treatment delivered intravenously was successful in treating a more advanced and inaccessible cancer in a mouse model using liposome-assisted drug delivery.

cellular components from a tumour's microenvironment – the tumour's immediate environment, including infiltrating cells and cancerous and non-cancerous elements, to conduct OV therapy. Macrophages are of interest as they present high in most tumour microenvironments. The team demonstrated that macrophages can successfully act as OV carriers for HSV-1 in the circulation. Systemically delivered OV therapy within macrophages can also cause tumour shrinkage and increased survival of animal models with an aggressive form of breast cancer called triple-negative breast cancer. Importantly, these results were obtained with a 100-fold lower viral load (the amount of virus in a person's blood), which lowers the possibility of toxicity-related events. These results show that OVs can be safely and effectively delivered in the circulation.

CHALLENGES OF ONCOLYTIC VIRUSES

Evading the immune response is one of the toughest challenges we face when delivering OV therapy using nanoparticles, says Howard, as cells of the immune system are constantly surveilling for foreign bodies like viruses. There is also a risk that nanoparticles within the circulation could result in non-specific uptake in tissues or neutralisation of the virus before it has reached the target organ, as the liver and spleen rapidly clear viruses in the blood.

The team overcame this concern by packaging and encapsulating an oncolytic adenovirus into CCL2-coated liposomes (a spherical sac-like vehicle comprised of organised fatty chains) so that it would be taken up by CCR2-expressing monocytes (immune cells) in the blood. This was an important step to reach the tumour as these monocytes usually home towards them. This OV and nanoparticle complex was very successful when administered intravenously in prostate cancer-bearing mice, with 1,000- fold less virus compared to using OV alone. Interestingly, significant reductions were described in tumours that had spread to the lungs and in the original growth in the prostate, suggesting that this OV treatment delivered intravenously was successful in treating a more advanced and inaccessible cancer in a mouse model using liposome-assisted drug delivery.

If OVs go undetected within the circulation, they must be able to accumulate at their target site, the tumour, and enter tumour cells next. According to Howard, to get the OV to the site that we want it at, we often use the signals to our advantage that cancer cells do not adequately respond to. One way to do this is to genetically modify the OV to increase the attraction of the virus to the tumour, for instance, by deleting the virus' genes which usually respond to cytokine-mediated immune responses. Alternatively, you can add binding sites to the surface of the nanoparticles, which bind to specific cancer cells which express or overexpress a particular molecular marker on their cell surface. However, this is insufficient to cure most cancers, as some do not have molecular signatures.

THE FUTURE OF OV THERAPY

As it stands, the current IT administration of OVs is not enough. More ambitious nanoparticle-OV complexes are required to overcome the obstacles of intravenous administration. Howard and her team have demonstrated that OV therapy paired with nanotechnology can deliver safe and efficacious results intravenously. The researchers also show that the tumour microenvironment can be used to your advantage to encourage the uptake of the nanodrug and to prevent clearance from the body to ensure it gets to the target tumour.

There remain concerns regarding the cost versus benefit of using nanoparticles and their safety, due to the materials used in the production that may cause adverse effects. However, nanoparticles are a growing field, with much more research still required, especially in more advanced cancers. Moreover, with a lot of nanoparticles being already approved and more in the works, it is an opportunity not to be missed in the advancement of upcoming cancer treatments due to their exciting prospects in helping patients with more complex and advanced disease.

Behind the Research

Dr Faith H Howard

E: f.howard@sheffield.ac.uk **W:** www.nanoncolytics.org Faith Nutter Howard @Nanobug_Shef

Detail

Bio

Dr Faith Howard is an award-winning early-career researcher at the University of Sheffield. She has previously worked in the biotech industry for the development of novel vaccines and contract research in the AMR field. Currently, Dr Howard's areas of interest are nanocarriers to improve targeted drug delivery to hard-to-reach and advanced cancers.

Funding

- Cancer Research UK
- Prostate Cancer UK
- Horizons Europe
- Team Verrico

Collaborators

Dr Munitta Muthana

References

- Howard, FHN, Iscaro, A, Muthana, M, (2022) Chapter Eight - Oncolytic viral particle delivery. In: Amiji, MM, Milane, LS, (Eds) *Systemic Drug Delivery Strategies. Volume 2 of Delivery Strategies and Engineering Technologies in Cancer Immunotherapy*, 211–230. Academic Press. doi.org/10.1016/B978-0-323-85781-9.00008-7
- Howard, FHN et al, (2022) Nanobugs as drugs: bacterial derived nanomagnets enhance tumor targeting and oncolytic activity of HSV-1 virus, *Small*, 18(13), e2104763. doi.org/10.1002/smll.202104763
- Iscaro, A, et al, (2022) Targeting circulating monocytes with CCL2-loaded liposomes armed with oncolytic adenovirus, *Nanomedicine: Nanotechnology, Biology, and Medicine*, 40, 102506. doi.org/10.1016/j.nano.2021.102506
- Kwan, A, et al, (2022) Macrophage delivered HSV1716 is active against triple negative breast cancer, *Future Pharmacol*, 2, 444–459. doi.org/10.3390/futurepharmacol2040029
- Howard, F, Muthana, M, (2020) Designer nanocarriers for navigating the systemic delivery of oncolytic viruses, *Nanomedicine*, 15(1), 93–110. doi.org/10.2217/nnm-2019-0323
- Ventola, CL, (2017) Progress in nanomedicine: approved and investigational nanodrugs, *PT*, 42(12), 742–755. www.ncbi.nlm.nih.gov/pmc/articles/pmc5720487
- Johnson, DB, Puzanov, I, Kelley, MC, (2015) Talimogene laherparepvec (T-VEC) for the treatment of advanced melanoma, *Immunotherapy*, 7(6), 611–619. doi.org/10.2217/imt.15.35
- Tinkle, S, et al, (2014) Nanomedicines: addressing the scientific and regulatory gap, *Annals of the New York Academy of Sciences*, 1313(1), 35–36. doi.org/10.1111/nyas.12403

Research Objectives

Dr Howard demonstrates alternative approaches for delivering drugs by wrapping sensitive agents like OV within nanobubbles for direct delivery to tumours.

Personal Response

What inspired you to conduct this research?

"A lot of drugs fail simply because they cannot reach their intended destination at high enough concentrations. It is known that less than 1% of the dose administered via the veins reaches its target, providing an exciting opportunity to enhance the effects of all sorts of drugs, including immunotherapies. Our team is pioneering packaging of sensitive biological agents such as immunotherapies within nanoparticles that also offer a navigation system for better targeting."

What are the next steps?

"In order to reach patients, the next steps are to scale-up production in a sustainable and environmentally friendly way. We aim to move away from traditional nanoparticle methods that require high pressure and harsh chemicals to improve efficiency and biocompatibility using bioinspired materials and embracing new manufacturing technologies."

Do you think we can expect big things from nanotechnology in the field of cancer research?

"Nanoparticles have been studied for decades, evidenced by the number of research articles at pre-clinical stages. Their translation to people has always posed regulatory/safety concerns; however, the mRNA liposomal COVID vaccine has started to pave the way for these much-needed changes and we now see a number of cancer vaccines using similar carriers moving towards clinical trials. There is a need for new materials together with more sustainable manufacture. As we gain more understanding of the regulatory standards required for approval of such materials, the hope is that anti-cancer drugs will reach their full potential using these delivery systems for the benefit of more patients."

University of Sheffield