Nanomedical Cancer Innovations

Nanoparticle treatments could prove a powerful new force against cancer

Nanomedicine is going to be big; really big. This rapidly emerging field of research is likely to have a massive impact on 21st century healthcare. Some scientists even compare it to the Industrial Revolution in terms of the impact it's expected to have. Billions of dollars are pumped into this field every year, and that investment is beginning to pay off as the first nanomedicines start to hit the shelves. Meanwhile, scientists are busy at work trying to uncover more about nanoparticles and how they could be used to address some of the greatest challenges of modern medicine; and one of the most formidable of these challenges is cancer.

About the same size as most natural biological molecules, nanoparticles have a number of qualities that make them excellent medical devices. They're very small, which means that they can pass easily through the body to the site of interest. What's more, their size, shape, and composition can all be adapted to suit different environments and purposes; this means that nanomedicine is extremely useful, particularly when it comes to cancer, where non-invasive, adaptable therapies are particularly important.

There are many ways that nanoparticles could prove a useful weapon in the fight against cancer. The particles could be used to carry drugs directly through to cancerous areas of the body, allowing stronger concentrations and smaller amounts of drugs to be administered. Nanoparticles might also be used as a contrast material to help identify tumours quicker, or as a form of thermal therapy, conducting heat so as to destroy unhealthy tissue.

Work currently being carried out at Diamond focusses on one area of nanoparticle cancer therapy that looks especially promising: using the particles to enhance the effectiveness of existing radiation treatments. Radiotherapy is a commonly used technique for combatting cancer, but there are some significant pitfalls.

Radiotherapy works by exposing the patient to radiation in the form of photons. The photons damage cancerous cells and can kill a tumour, but they also have a very narrow therapeutic window; this means that the amount of radiation needed to destroy the cancer can be very close to, if not more than, the amount that also kills lots of healthy cells. That's why patients often start feeling really unwell, and if a patient needs more radiation that can safely be administered without killing too many healthy cells, then radiotherapy ceases to be an option.

But nanoparticles could help to change this situation. They react intensely to photons, damaging surrounding cells; this means that they could enhance and better target radiation treatments so that much less exposure has a greater effect. This approach has an added advantage because the facilities are already in place. Doctors would simply need to introduce nanoparticles to the site of the tumour prior to beginning radiation treatment. This small addition to the current process could dramatically improve the effectiveness of radiotherapy. At it's heart the idea is really quite simple – the nanoparticles increase the chance of a successful medical outcome whilst leaving the chance of there being any difficulties about the same. This then results in a much greater chance of cure without complication and a wider 'sweet spot' in terms of the treatment plan.

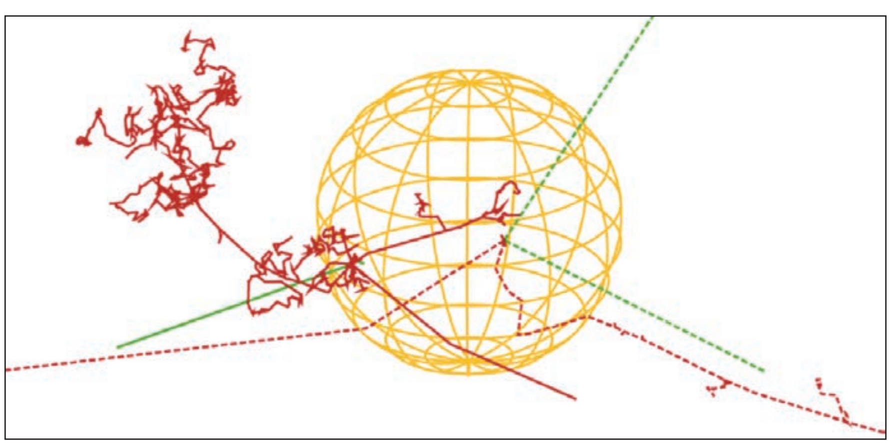
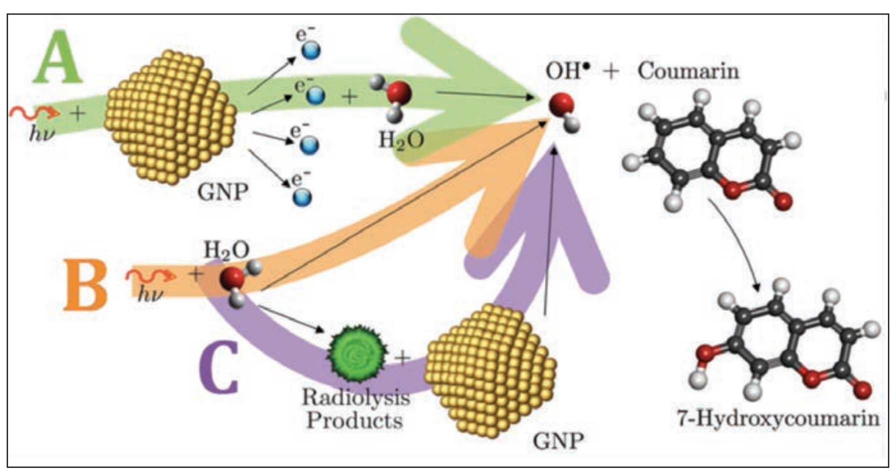


Illustration of the kinds of processes that can occur when an X-ray (shown in green) interacts with a gold nanoparticle, illustrated by the yellow sphere. Many electrons can be created. These are illustrated by the red lines. One interaction takes place deep inside the nanoparticle and is illustrated using dotted lines. A second interaction is shown nearer the nanoparticle's surface and is illustrated by the solid green and red lines. Figure taken from S.J. McMahon et al. Biological consequences of nanoscale energy deposition near irradiated heavy atom nanoparticles. Sci. Rep. 1, 18; DOI:10.1038/srep00018 (2011).

More work is needed to bring this research into a clinical setting, and the first step towards developing effective nanoparticle cancer therapies is to work out how exactly they kill tumours. Using Diamond's I15 and B16 beamlines, Professor Fred Currell and his team from Queen's University Belfast have determined that the process begins when photons from the radiation treatment knock electrons off of the atoms inside the nanoparticles; a chain reaction then causes many other electrons to leave the atom, resulting in a release of energy that destroys surrounding cells. This makes the radiation treatment much more localised and much more effective.

Fred likens this chain reaction to a kind of 'Atomic Jenga'. "We use the X-ray to take one electron our from a collection of electrons piled up inside one of the nanoparticles." He explains. "Just like in Jenga, this can make the whole system unstable – the result is lots more of the electrons collapse down. However, this version of Jenga has to obey the rules of Quantum Mechanics and this means that when some electrons fall towards the centre of an atom others escape." It is these escaping electrons that seem to act together to provide a very local, nanoscopic, boost to the biological effects seen. If the nanoparticles are only in the tumour then this boost is only there too.

Radiation treatments also cause a chemical reaction that transforms water in the body into a more toxic molecule called hydroxyl (OH). It is well known that OH is responsible for about 70% of DNA damage, and hence cancer cell death, in conventional radiotherapy. The addition of nanoparticles could potentially increase the amount of OH produced in a localised area, increasing the effectiveness of the radiation. One of the big surprises for Fred's team was finding an entirely new and unexpected way of making OH. Our bodies are mostly composed of water so looking at what happens when nanoparticles and water are exposed to X-rays together makes a good starting point. Fred's team did this by making up samples containing just water, nanoparticles and a molecule called coumarin. The coumarin catches any OH produced, providing a permanent record that can be picked up after the exposure to the X-rays is finished.



Different ways the X-rays can make OH. Arrow A shows the 'Atomic Jenga' type of event. The electrons that escape then go on to cause chemical reactions in the surrounding water with the result being OH formation. Arrow B shows reactions occurring in the water without involvement of any nanoparticles. Arrow C shows the previously unknown way of making OH. Some products (still unknown) produced when the water is exposed to X-rays then seem to interact with the nanoparticles to produce lots more OH. Figure taken from C. Sicard-Roselli et al. A New Mechanism for Hydroxyl Radical Production in Irradiated Nanoparticle Solutions. Small DOI: 10.1002/smll.201400110 (2014).

Diamond enables the scientists to separate out the contributions of these processes. Once of the big findings here is that the nanoparticles can lead to lots more production of the

OH than was previously expected. This is good news since it hints at the possibility of delivering still more tumour-kill whilst leaving the healthy parts of the patient unaffected. What's more, the synchrotron allows the team to adjust the energy of the photons being emitted; this means that they can expose nanoparticles to photons carrying different energies and observe how the behaviour of the particles changes. The team's goal is to identify mechanisms at work that will in turn indicate the perfect size and composition of nanoparticles.

But this is no simple feat. There are many different kinds of cancer and the type of nanoparticle and radiation dose that tumours respond to is different depending on the variety of cancer you're working with. Fred and his team are currently focussing on breast, brain, and prostate cancer, but they hope to eventually create therapies for a wide variety of different cancers.

Fred observes why I15 and B16 are so useful in this work: "Diamond gives us something we can get only at a synchrotron. By using the machine to precisely manipulate the energy that hits the nanoparticles, I can turn on and off certain processes, test hypotheses and, ultimately, point the way to developing more effective therapies." He continues: "Modern medical research often starts with fundamental atomic processes and that's what we're doing here."

Radiation of course has to be handled with respect and stringent safety measures are in place at Diamond. Fred's team have built up some robotic systems with which to safely handle the samples. Everything is controlled in a safe environment robotically whilst the team monitor the experiment's progress using cameras. The team grew rather attached to one of their robotic systems, which they now nickname Mjolnir. Readers conversant with Nordic mythology you will know that Mjolnir is Thor's hammer and indeed the apparatus does look a bit like a giant hammerhead. However, the team have another reason for this name, to them it also stands for **M**achine to **J**udge the **O**utput of **L**ight-**N**anoparticle **I**onizing **R**eactions.

Chris Polin, one of the research team, loading Mjolnir up with a set of samples before they are exposed to Diamond light.

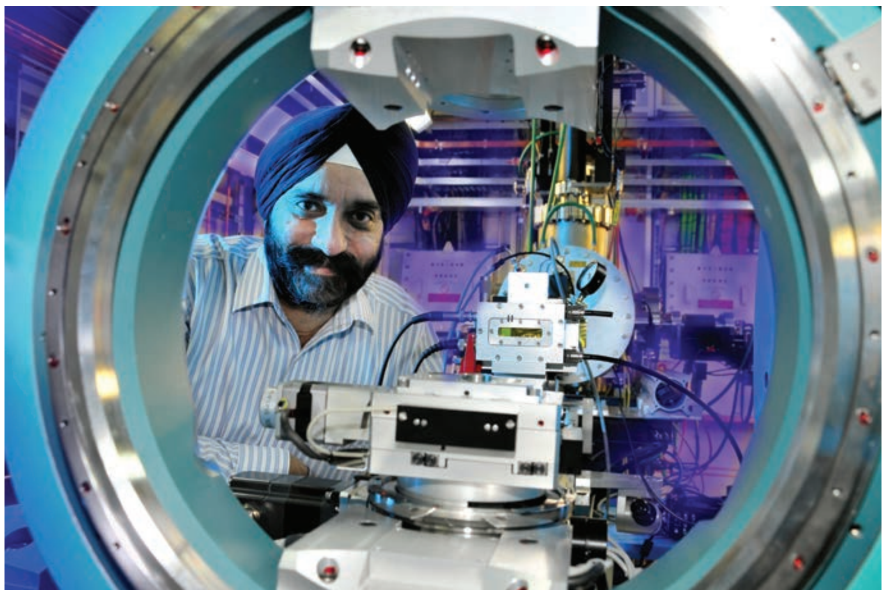
Nanoparticle cancer treatments are already in clinical trials, but the work of Fred and his team could help to further improve the effectiveness of these next-generation therapies. Fred is well aware of what his research could mean for patients. He explains: "My daughter became ill some years ago. I was sitting in the hospital feeling very useless, but seeing amazing feats of science and technology saving her life. This got me thinking – 'you can contribute to this'."

And so Fred moved from studying fundamental physics to researching novel cancer treatments. "The science I was doing before was important and fascinating, but I suppose I just began to feel a sense of urgency with these issues. The skill set I'd developed from fundamental physics gave me a really useful perspective, and I think it's helped me to push forward some important discoveries about the way nanoparticles behave at the atomic level, and how we can harness that behaviour as a cancer therapy."

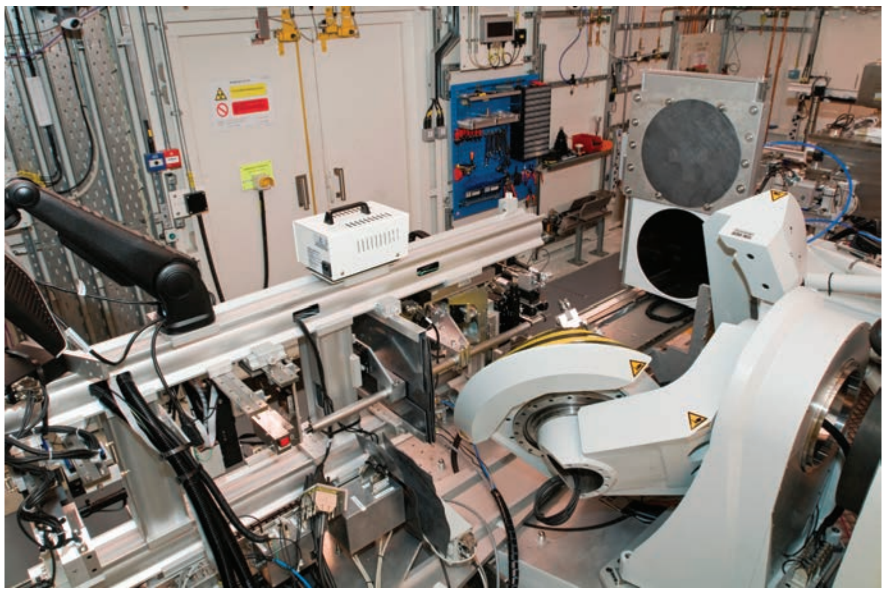
Large parts of the nanomedicine revolution are taking place without people considering X-rays. However, as new nanomedicines come on line, doctors aren't going to stop taking X-ray photographs of patients – X-rays are used more than anything else to make medical images. This suggests that the combination of X-rays and nanomedicines should be considered together early on in the research process. Here facilities like Diamond, coupled with systems like Mjolnir have a big role to play.

Fred concludes: "If we get this right, it will help people for years to come, well beyond my lifetime. I think it's the idea that this research will go on to benefit our children's lives and their children too; that's the best thing for me. That makes everything completely worthwhile."

Fred and his team are part of one of the most important medical movements in history. Their work could redefine the way we approach cancer therapy and significantly improve the way those therapies impact on the lives of patients. There's still work to be done, but it looks as though nanoparticles have the potential to augment current cancer therapies and improve outcomes for patients; and for people like Fred who dedicate their lives to cancer research, that is most certainly a cause worth striving for.



Kawal Sawhney, Principal Beamline Scientist, using the B16



I15 Beamline

I15 Beamline

Contact and author: mary.cruse@diamond.ac.uk