CHIEF SCIENTIST OFFICE

CODE:TCS/16/07

RESEARCH PROJECT BRIEFING

TITLE – Optimising nanoparticle-based targeted radiotherapy molecules

AIMS

- Targeted radiotherapy involves administering, intravenously, particles that have an affinity (by targeting) for cancer cells and are sufficiently radioactive to kill the cells. Particles are targeted using antibodies specific to molecules on the surface of cancer cells. These can be attached along with the radionuclides to gold nanoparticles which act as a platform.

The aims of this project were to:

- Construct targeted nanoparticles and characterise their physical (including size) and chemical properties and determine their uptake and distribution in cancer cells
- Optimise the radiolabelling (attachment of radionuclides) to maximise cancer cell kill
- Determine the amount of radioactive particles that are required to kill cancer cells.
- Characterise the binding of the particles to cancer cells
- Determine the bio-distribution of the particles and the dose to tumours in vivo
- Optimise particle size based on bio-distribution data

KEY FINDINGS

- The particles distributed throughout the cytoplasm of the cancer cells but didn't enter the nucleus so can be loaded with radionuclides that produce medium and low energy emissions but not very low energy ones such as Auger emitters.
- Radiolabelling carried out after functionalising the particle increased radionuclide loading
- Dosimetry measurements demonstrated a dose-response relationship similar to that with external beam sources i.e. a 50cGy to 10Gy to produce a 20% -100% cancer cell kill.
- Bio-distribution studies demonstrated very high liver activity due to the particle size
- Small particle fabrication was carried out by inclusion of copper ions during nanoparticle preparation to facilitate production of much smaller particles that will not accumulate in liver.

WHAT DID THE STUDY INVOLVE?

Gold nanoparticles, fabricated in the lab and commercially sourced, were functionalised by adherence of linkers for antibodies and radionuclides. The optimum order of functionalisation and addition of radionuclides was determined using a range of analytical chemistry techniques including electron microscopy and Ramon spectroscopy. In vitro cell studies along with dosimetry were used to characterise the particle binding to cancer cells and cancer cell killing doses of the particles. Particles were injected n mice and the bio-distribution determined by measuring organ and tumour uptake. Autoradiography was used to visualise dose distribution across tumours.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

- Physico-chemical characteristics: The particle overall size increased with addition of targeting groups (Erbitiux) and radiolabelling and we were able to determine the optimum sequence for this functionalisation process. The particles distributed throughout the cytoplasm of the cancer cells but didn't enter the nucleus which means that they are not suited to the delivery of Auger emitters which need to be incorporated into the nucleus to be effective.
- Radiolabelling carried out after functionalising the particle increased radionuclide loading which is essential for delivering high dose radiation to cancers.
- Dosimetry measurements demonstrated a 50cGy to 10Gy to produce a 20% -100% cancer cell kill. This corresponds to typical results using external beam radiation sources.
- Bio-distribution studies demonstrated very high liver activity due to the particle size which would not be acceptable in patients so we developed much smaller particles.
- Small particle fabrication was carried out by inclusion of copper ions during nanoparticle preparation which will form the basis of future targeted radiotherapy development work.

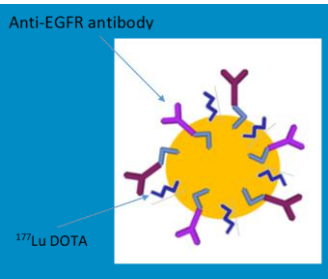
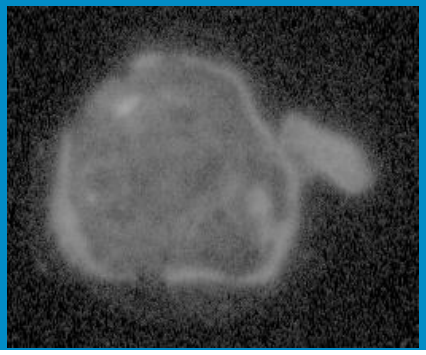


Diagram showing functionalised gold nanoparticle with radionuclide 177Lu and targeting antibody



Autoradiograph of 50uM section of xenograft from (4h after injection of EGFR-targeted 177Lu-NP) showing heterogeneity of dose distribution.

WHAT IMPACT COULD THE FINDINGS HAVE?

- We have demonstrated that targeted gold nanoparticles are suited to the delivery of a range of radionuclides to cancers and are cytotoxic to cancer cells. To be translatable the particles need to be small enough to be excreted through the kidney and we have produced very small nanoparticles which could be utilised for this purpose.

- Nanoparticles within the size range that are excreted by the kidney rather than the liver can be toxic so studies that ensure that the functionalisation of the nanoparticles decreases their toxic risk are required prior to translation.

HOW WILL THE OUTCOMES BE DISSEMINATED?

1) The physico-chemical results from the study have been published:
Cabello G, Nwoko KC, Mingarelli M, McLaughlin AC, Trembleau L, Feldmann J, Cuesta A, Smith TAD. Physico-chemical tools: towards a detailed understanding of the architecture of targeted radiotherapy nanoparticles. ACS Applied Bio-materials 2018 1: 1639-1646

2) Paper on production of Cu/Au nanoparticles: J. Alloys & Cmpds: Cabello G, Nwoko K, Marco J, Sanchez M, Mendez A, Feldmann J, Yanez C, Smith T. Cu@Au self-assembled nanoparticles as SERS-active substrates for (bio)molecular sensing (in press)

The next piece of work will be based on the use of the small Cu/Au nanoparticles

CONCLUSION

Functionalised gold nanoparticles are a convenient system for delivering radiation to tumours. Ultra-small gold nanoparticles that will be excreted through the kidney can be fabricated by inclusion of Cu ions during their manufacture.

RESEARCH TEAM & CONTACT

NAME or NAMES: Dr Tim Smith, Dr L Trembleau, Prof A McLaughlin and Dr G Cabello

Address. University of Aberdeen

t.smith@abdn.ac.uk

01224 437822

Thank you to the CSO for funding our research into targeted radiotherapy