Targeted cancer cure using nanoparticles
Jonathan Lee
Supervisors: Dr. Megan Lord, Dr. Brooke Farrugia and Prof. John Whitelock
Research Theme: Resources and Infrastructure for the Future

Background and Motivation
• Ovarian cancer is ranked as the fifth leading cause of cancer-related deaths among women, and the leading cause of death from gynaecological cancer [1].
• This high mortality rate is due to the difficulty at diagnosing the disease at an early stage and the persistence of dormant, drug resistant cancer cells which cause relapse.
• Current treatments for ovarian cancer consists of surgery to remove the bulk diseased areas followed by chemotherapy, both of which are highly invasive and non-targeted, resulting in unnecessary damage to non-cancerous cells.
• Recent research has found that nanoparticles for targeted cancer drug delivery can show promising results.
• In order for targeted drug delivery to work, the active cell requires using ligands to bind to receptors present on cells.
• By conjugating the surface of cerium oxide nanoparticles (nanoceria) with active cell selective molecules such as heparin, targeted drug delivery for cancer patients can be achieved.
• This could ultimately result in faster acting, less invasive treatments to combat the spread of the cancer, improving the chance of the patient to fully recover.

Aim
To functionalise nanoceria with heparin using an organosilane linker APTES in order to investigate the biological activity of these particles against ovarian cancer cells.

Method and Results

1. Do these nanoparticles get taken up by the cancer cells? [Fluorescence Microscopy]

2. Do these nanoparticles kill the cancer cells? [MTS Assay]

3. What effect do the nanoparticles have on the cancer cells? [Flow Cytometry]

Fig 1: Schematic of the approach used to functionalise nanoceria with heparin using (A) 3-aminopropyltriethoxysilane (APTES) as the linking molecule to allow carboxylic acid groups on heparin to react with free amino groups on the surface of nanoceria via an EDC coupling reaction [2].

Fig 2: Cell viability of bare nanoceria, LMWH-nanoceria and HMWH-nanoceria compared to cells exposed to medium only (control proliferation), analysed over a period of 72 h. Assay showed that the heparin conjugated nanoceria lead to a decrease in cell proliferation when compared to the control at all concentrations.

Fig 3: Fluorescence microscopy of:

A) Cells + Media (Control)
B) Cells + LMWH-nanoceria
C) Cells + HMWH-nanoceria

Red: Cytoskeleton
Blue: Cell nuclei
Green: Heparin uptake

Both LMWH and HMWH have been uptaken by the cancer cells as indicated by the green dots.
More green dots in LMWH sample indicating higher uptake.

Fig 4: Analysis of oxidative stress, as measured by the dye DCFH-DA, of ovarian cancer cells exposed to nanoceria, LMWH-nanoceria or HMWH-nanoceria compared to cells exposed to normal growth conditions after 72 h.
A) Nanoceria was uptaken the most, whilst heparin-nanoceria was uptake the least (although still a high amount).

Conclusion
• Heparin was successfully functionalised onto the cerium oxide nanoparticles.
• With respect to biological activity, heparin-nanoceria has shown great promise in limiting cell growth in the ovarian cancer cells.
• LMWH-nanoceria was shown to uptake much more effectivity than HMWH-nanoceria at both concentrations (25 μg/mL and 50 μg/mL).
• Heparin-nanoceria caused greater oxidative stress compared with nanoceria alone in cancer cells, leading to increased cell death as supported by the MTS assay

References

What does this all mean?
Cancer cells take up the heparin-nanoceria → Oxidative Stress → Kills the cells