YARM SCHOOL

DESIGNING DRUG ENCAPSULATED NANOPARTICLES TO REVERSE THE UNDERLYING CAUSE OF CORONARY HEART DISEASE

By Darshan Prabhakar, Kieran Gill, Ananya Singh, Noah Bickenson, Ben Thompson & Sarah Mhando (Yarm School)

WHY WE CHOSE THIS TOPIC:

We were all interested in how nanoparticles can precisely deliver drugs to cancer tumours, having read about it in a science magazine. Hence, we wanted to apply this concept to coronary heart disease. We thought that the current treatments do not do enough to tackle the underlying cause of the disease, and that this was an innovative alternative with a large amount of potential.

INTRODUCTION:

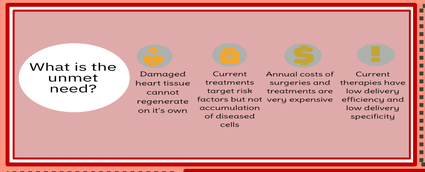
Nanomedicine is an emerging field which uses very small particles that are 1-100nm in size. The applications of nanomedicine are mostly used in the treatment of cancer but the exciting properties of nanomedicine have huge potential to be feasibly rolled out in the treatment of coronary heart disease in the long-term future of the NHS.

Our strategy uses nanoparticles, which have special properties that allow them to 'cage' drugs and precisely target areas of the body - such as plaques in arteries.
Nanomedicine has the potential to maximise the benefit and minimise the risk of drug therapies.

There are 7.6 million people living with heart and circulatory diseases in the UK. With more than 100,000 hospital admissions due to heart attacks, it is imperative to develop innovative strategies that make the most of developing technology. The main goal of our strategy is to treat the underlying cause (atherosclerosis) of coronary heart disease, not the symptoms or risk factors. Our treatment will bridge the gap between lifestyle modifications and invasive procedures.
We aim to utilise nanomedicine in order to safely, effectively and precisely break down the plaque blocking the arteries, thus reducing the number of patients having to take lifelong statins/life-threatening procedures.

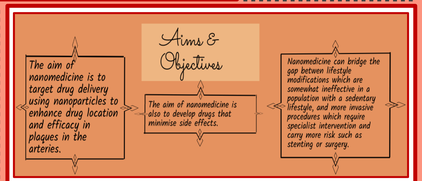
Coronary heart disease remains one of the UK's leading causes of death, and is the most common cause of premature death in the country. Current drug therapies in the NHS have low delivery efficiency, and poor target specificity.

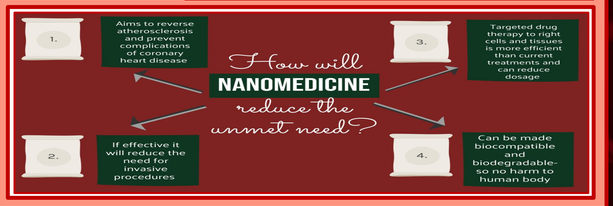
WHAT IS THE UNMET NEED?



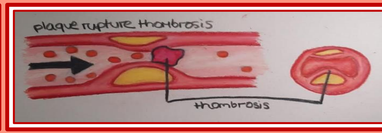
Surgical procedures such as stenting or bypass surgery are invasive and risky, and are only temporary solutions that do not prevent the underlying cause of coronary heart disease.

The incidence of coronary heart disease is projected to increase in the next decades due to an ageing population, and a rising prevalence of risk factors such as obesity and diabetes.





CORONARY HEART DISEASE:



Plaque forms from various substances that flow through the blood e.g. calcium, cellular waste, fibrin, fat and cholesterol. Atherosclerosis occurs because the arteries narrow and harden due to plaque. Plaque build-up occurs because of damage to the arterial walls which enables the deposition of plaque. This damage seems to occur because of cigarette smoke, diabetes/elevated blood sugar levels, obesity, sedentary lifestyle, genetic conditions (familial hypercholesterolemia), high levels of 'bad' LDL cholesterol and low levels of 'good' HDL cholesterol. In response to plaque build up, white blood cells are sent which turn into foaming cells which secrete substances like more fats which in turn causes more inflammation. Muscle cells then multiply and form a cover over the area. This leads to coronary heart disease as narrowing of the arteries reduces blood flow and increases risk of heart attack/stroke.

Normal Artery – blood can flow through.

Plaque has built up – blood can't flow through.

ARTIFICIAL INTELLIGENCE:

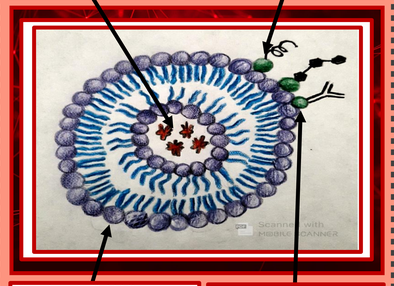
AI predictive modelling system can help prioritise which patients receive the plaque-reducing nanotherapy. We understand that any drug in development can be initially expensive so it is important to prioritise which patients receive it based on clinical need. An AI algorithm using patient data already available in NHS databases and can estimate the risk of a heart attack in patients with coronary heart disease. This could be used by both radiologists and cardiologists, in order to diagnose patients more accurately and select patients who would benefit the most from nanomedicine. AI also has potential to create a 3D image of a patient's heart and identify potential blockages which may cause heart attacks. This improves the current angiogram diagnostic procedure and can further improve how cardiologists can prescribe the plaque-reducing nanotherapy to patients in the near future.

POTENTIAL ISSUES:

Since nanoparticles are so small they could end up entering parts of the body where they could be potentially dangerous. For example, there may be risk if nanoparticles are inhaled, swallowed or absorbed through the skin. Since nanoparticles are small they may cause irritation in the lungs if inhaled and cause damage similar to the effects of breathing in fine dust. Toxicology testing has shown liposomal formulations to be less toxic than drugs alone, but further toxicology studies are needed under more realistic conditions and concentrations.

THE LIPOSOME:

Liposomes are made of phospholipids which are the main components of cell membranes. This is a benefit as the liposome can avoid detection by the body's immune system. Liposomes can be naturally derived, and are biologically inert. Extensive toxicity screening of liposomes have shown them to be generally safe for pharmaceutical use, but this does not negate the need for extensive clinical trials as we propose to use a modified liposome. The liposome encloses the drug and protects the drug as it travels through the bloodstream to its intended site.

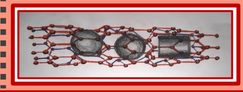


HOW IT WORKS:

Atherosclerosis is a precursor of coronary heart disease. This is the build-up of plaque in the walls of the arteries. The build-up can lead to a blood clot forming in arteries, thus leading to a heart attack. Within the plaque there is a necrotic core, consisting of dead and damaged cells. These cells produce a much higher concentration of a signalling molecule called CD47 that prevents macrophages from clearing up the plaque. This is known as the 'cloaking signal' which allows the plaque to grow in arteries without being cleared up. Our aim is to create drug encapsulated liposomes that turn off the upregulated CD47 signals expressed in the plaques. This will then allow macrophages, cells part of the immune system, to ingest or 'eat' the plaque.

PROPERTIES:

We propose to use liposomes as our nanoparticle. The lipid casing around the drug would protect the drug as it travels around the bloodstream to the plaque in the artery. This encapsulation will prevent early degradation and dilution in the bloodstream.
The surface of the liposome allows different molecules to be attached such as a dye to track the liposome around the body. This will be especially useful in the clinical trial phase to ensure the drug is delivered to the right location.
The liposome would need surface receptors that have a complementary shape to the receptors found uniquely on foam cells in plaques in arteries. This would allow the liposome to bind to the plaque only. The binding of receptors would cause the lipid envelope to break down and release the drug to the CD47 molecules to inhibit them and turn off their 'cloaking signals'.
Other nanoparticles can be used as drug delivery vehicles such as carbon nanotubes (shown below) which have shown promising potential in loading multiple drugs to specific locations in the body e.g. in cancer treatment.



STEPS TO IMPLEMENTATION:

STAGE 1 2 & 3 TRIALS:

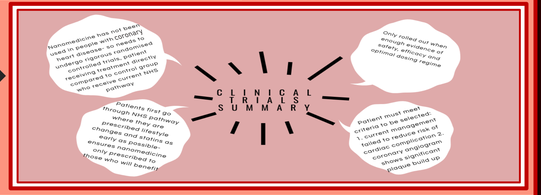
First, in vivo and in vitro trials need to happen in test tubes and animals to check if it's safe. Then, stage 1 trials occur where it's tested on a small sample of healthy humans to check the safety and appropriate dosage. Next, it will enter stage 2 trials with a few hundred people with atherosclerosis to determine short-term side effects and efficacy. It can then enter stage 3 with thousands of patients to test efficacy and safety over a long period of time. If successful here it can begin mass manufacture.

HOW THE TRIALS WORK:

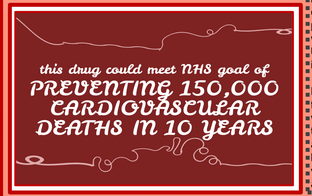
To ensure the drug's safety in patients, it must undergo randomised control trials. The group receiving the new drug must be compared to a control group receiving current NHS treatment. The trial needs to be randomised and double blind to ensure there is no bias.

CLINICAL TRIAL SELECTION:

Initially the trial will test on 40-65 year olds. This reflects the population we wish to use the drug in and also ensures we have a wide age range to participate, so the results are more accurate. The treatment aims to prevent heart attacks and other cardiac complications which are a major source of mortality and morbidity.



HOW WE WOULD MAKE IT AVAILABLE:



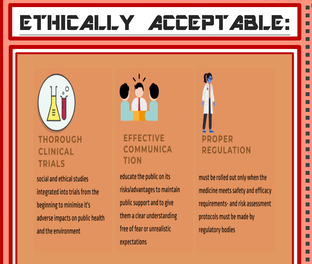
During the clinical trials the drug would be administered by a cardiologist, who would measure the reduction in plaque during treatment by using a coronary angiogram. The end goal would be that our drug would be made available via intravenous injection by specialist nurses at general practices, once lifestyle modifications have been tried and proved unsuccessful. Given this we can tap into the wide-reaching network of primary care throughout the UK - giving all who need it equal access to the injection.

Ideally, an agreement would be made with Big Pharma for the mass production of the treatment. The injection will be continued regularly until an angiogram proves that there has been a significant reduction in plaque, and we can also utilise the infrastructure which has been recently established as a result of the COVID-19 vaccine rollout for a swift and effective administration.

AFFORDABLE:

Initially, the liposomal drug formulation will be expensive to manufacture like all new drugs. We would expect as new manufacturing methods are found, the cost of manufacture would gradually decrease. If effective, we would expect that the benefits outweigh the cost in the mid to long-term. Less patients will go on to have a heart attack and develop costly complications such as heart failure. As our proposed drug aims to reverse atherosclerosis, once the drug has reduced plaque to a healthy size, the drug would not need to be taken as frequently as current drugs such as statins are taken further reducing cost. Although initially intravenous injection is the most feasible method of administration, developing an oral tablet would be cheaper but the liposome must be modified to cross the intestinal epithelium and not be broken down by acid and enzymes in the gut.

ETHICALLY ACCEPTABLE:



Patients should be clearly briefed on how the medicine works and any potential side effects so doctors can obtain informed consent to taking the medication, as autonomy should always be a priority. This is important to gain and maintain public support. Doctors must follow the 4 pillars of: beneficence, non-maleficence, justice and autonomy when assessing each patient they prescribe the medication to.
The use of artificial intelligence to select patients for the trial/treatment comes with certain ethical issues – such as personal data being used. Their permission would explicitly have to be given beforehand, and the creation of any A.I. algorithm which contains patient data should be anonymised.

ACKNOWLEDGEMENTS:

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