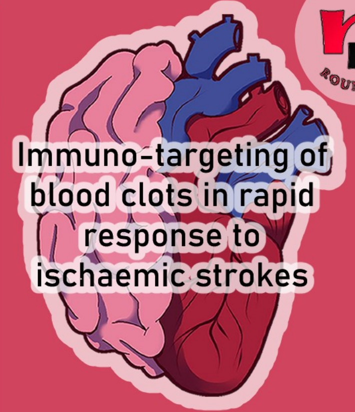
Immuno-targeting of blood clots in rapid response to ischaemic strokes



Introduction

Ischaemic strokes are the most common form of stroke. They occur when a blood clot blocks the flow of blood and oxygen to the brain, causing the brain tissue to die. Ischaemic strokes often leave the patient with complications long after the event.

How Serious a Problem?

- Every year in the UK, 100,000 people suffer an ischaemic stroke
- 38% of these cases prove fatal.
- The PHE predicts that 1 in 6 people in the UK will suffer a stroke in their lifetime.
- Strokes cost the NHS an estimated 4.6 billion per year.

Current Treatments

Hospitals use a range of treatments when tackling ischaemic strokes.

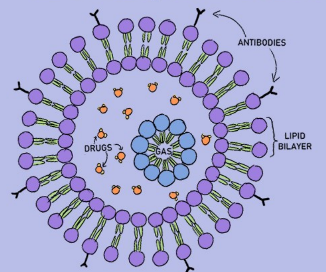
- Examples of medication used include anticoagulants, platelet inhibitory drugs, injection of thrombolysis medication.
- Patients are also prescribed long-term drugs
- Surgical procedures like thrombectomies or carotid endarterectomies are dangerous, invasive surgeries.

Our aim is to develop a medication-based treatment to be used on patients immediately after an ischaemic stroke. It will take effect rapidly, eliminating the risks associated with invasive and potentially dangerous surgery, and limiting the long-term effects suffered by stroke survivors.

Targeted Drug Delivery - Why Liposomes?

Our treatment uses targeted drug delivery through echogenic immunoliposomes (ELIPs). These are preffered because:

- They are able to pass through the physiological barriers like the blood-brain barrier, stratum corneum, and vascular endothelium due to their lipid bilayer.
- ELIP's conjugate the advantageous properties of micro-bubbles and liposomes. They allow for loading of high drug dosages and the gas core enables US imaging and triggered release of encapsulated drugs via ultrasound, which allows for greater spatial accuracy.
- They can be bound to antibodies that are able to identify and attach to the blood clot in the brain.
- The anitbody anti-insoluble fibrin antibody (clone 102-10) can be attached to the surface of the liposome. It binds specifically to insoluble fibrin, which is the major structural component that makes up blood clots. This anti-body has only been proposed for cancer treatments so far, but the properties of insoluble fibrin is the same in blood clot formation.



Ultrasound Triggering

Our proposal utilises ultrasound to trigger drug release because:

- It is an exogeneous physical stimulus, enabling drug delivery and duration to be more closely controlled.
- There are less interpatient variations, unlike with endogeneous triggering.
- Due to the echogenic properties of ELIP's, they can be used as both imaging contrast agents and drug delivery vehicles via ultrasound.
- Unlike current stroke surgeries, (eg. thrombectomy), it's non-invasive, and therefore much safer.
- It is already widely used for other treatments/therapies due to how non-invasive, safe and cost effective it is.

What drugs are in the liposome?

Alteplase:

- It is a tissue-type plasminogen activator (tPA), activating plasminogen to form plasmin. Plasmin breaks down the fibrin mesh (the blood clot's structural support).
- It's already approved for thrombolysis in patients who present for treatment within 3 hours.

Asprin:

- It's the anti-coagulant adjunctive used alongside tPA's in thrombolysis.
- It blocks cyclooxygenase-1 (COX-1) in platelets, which prevents them from activating and forming a clot.

Clinical Trialling

- The drugs we will use (alteplase and asprin) have been approved and are already in use.
- Our clinical trialling won't test for the efficacy of the drugs themselves, but rather will test the liposome and ultrasound trigger in relation to targeted drug delivery.
- We will also use the clinical trials to establish dosage, ultra-sound frequency, and time needed for the drugs to circulate.
- Finally, our trials will be useful in establishing whether any interpatient variation affects the treatment, method, or results.

1. To ensure there are no negative impacts of having our liposomes in the body, we will first test the liposome solution in vitro on tissue samples in test tubes and in vivo on mice.

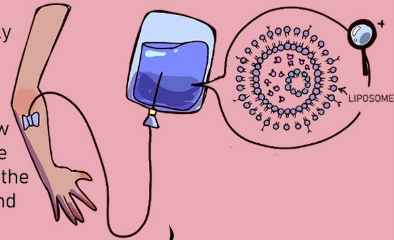
2. Once toxicity has been checked, and the liposomes are approved for stage 2 trialling, a small group of healthy volunteers will be given the drug in order to test for safety and/or ensure there are no unforseen side effects.

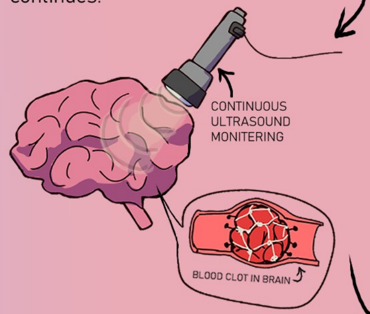
3. Next, we till test the drug on a larger number of people (100-200) with blood clot problems like deep vein thrombosis. We will compare to standard treatments to test the efficacy of the drug delivery system and whether it can be proven to be faster acting.

4. Then, testing on different groups within the population will be carried out to test for any interpatient variation.

5. Finally, once the drug has been approved for use, it will slowly be introduced into the NHS. First, in hospitals found to have the highest cases of stroke admission, then slowly into other hospitals once the initial implementation proves succcessful.

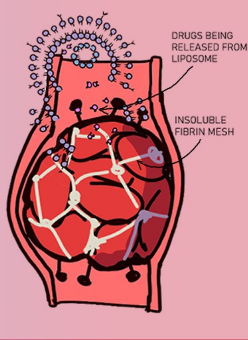
1. Inject intravenously a buffered isotonic solution containing the liposomes. The patient is left to allow the drugs to circulate for 10 minutes while the continuous ultrasound imaging of the brain continues.





2. Through functional ultrasound imaging, the progress of the liposomes through the brain can be monitered due to the microbubble within the liposome, which is an ultrasound contrast agent.

3. Once the liposomes are observed to have stopped moving (indicating they have attached to the blood clot in the brain), an ultrasound pulse is sent through the cranium and the aqueous contents of the liposome are released



4. The alteplase catalyses the break down of fibrin, and the asprin aids in thinning the blood to speed up the rate at which the blood clot is dissolved. Blood circulation to the brain is restored. The drugs contained in the liposome will work their way out of the body naturally.

Meet the team:

Tara Conway-Shah *(Biology, Chemistry, Maths):*
→Team Leader: researched method, drugs and feasibility.
Stefano De Marchis *(Biology, Chemistry, Psychology):*
→Lead Researcher: proposed and researched liposome+ultrasound.
Sehar Majeed *(Biology, Chemistry, Maths):*
→Insight into: economics, ethicacy, efficacy, feasibility
Fionn Robinson *(Biology, Chemistry, Maths):*
→Editor, Researcher: researched stroke and context, fact checked
Sophia MacDonald *(Biology, Chemistry, Maths):*
→Artist: poster design, layout
Jack Fearn *(Biology, Chemistry, Maths, Further Maths):*
→Implementation: clinical trialling, background research into NHS

Social Acceptability/Ethicacy:

- The proceedure is non-invasive and theoretically poses an improved method for treatment of strokes. The only potential cause for social adversity we see is that liposomes are a relatively new treatment, which may be cause for anxiety for some.

Efficacy:

- The efficacy of alteplase and asprin have already been proven. The efficacy of the liposome and ultrasound trigger will be tested during clinical trialing.

Feasibility:

- Liposomes have yet to pass the trialling stage, though they are one of the front-runners of novel drug delivery methods. We believe liposomes will be approved for use within the next ten years.

Economics:

- While the average cost for a mechanical thrombectomy ranges from £8,000-£13,000 in the NHS, we predict our treatment, once implemented, will cost between £300-£600 (based off how much an ultrasound currently costs in the NHS)
- The cost of lipsome manufacturing is high due to expensive raw materials used in lipid excipients and expensive equipment
- Based on the median costs of producing a liposome through sonication-lyophilization-rehydration and the cost of producing one dose of the Moderna Covid Vaccine (which was liposome-based), we predict synthesis of one dose (dosage to be confirmed through trialling) of the drug will cost between £400-£800.
- However, we still believe our treatment will save the NHS money in the long-term