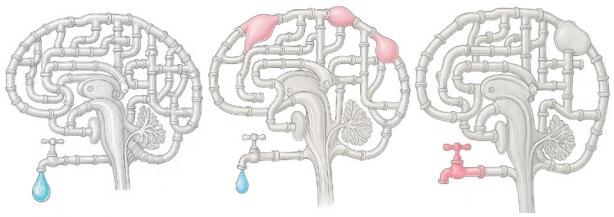
FLOWCODE: Mapping the Brain's Plumbing System to Halt Swelling and Slow Neurodegeneration

In the 5 minutes it takes to read this concept note, 100 people across the world will have been diagnosed with dementia. Over 60 people will have been hospitalised with a traumatic injury to their brain or spinal cord, 10 of them will die, and another 20 will suffer debilitating secondary injury because of uncontrolled brain swelling. Sadly, there are few interventions that can stop this from happening. What links these devastating conditions is the disrupted flow of fluid through the brain and spinal cord (the central nervous system or CNS). When CNS fluid builds up acutely after injury, this leads to swelling and increased damage; when there is too little flow as we age, the CNS fluid cannot wash away the toxins that accelerate neurodegeneration. We currently know very little about how the components that control the recently discovered CNS 'plumbing system' work. FLOWCODE will fill this critical knowledge gap by creating dynamic 'plumbing maps', allowing us to model CNS fluid flow in health, injury and disease for the first time. Identifying which valves are critical will lead to new diagnostics and therapeutics for understanding fluid movement through the CNS, allowing us to open or close the right 'valves' at the right time. This will create new interventions that enable us to diagnose, control and minimise brain swelling, maximise recovery and reduce the incidence of neurodegeneration.

1. WHAT AM I TRYING TO DO?

When we sleep, CNS fluid flow increases, clearing away waste products and preserving brain health. However, as we age, night-time CNS fluid flow is slower than in youthful sleep, causing the waste products linked to neurodegeneration (such as amyloid and tau proteins) to accumulate in our brains. Traumatic injury, stroke, infection or neurosurgery can also more acutely disrupt CNS fluid flow. In those cases, CNS fluid floods into the injured tissue, causing it to swell. The dramatic build-up of pressure in the skull can quickly become life-threatening. Globally, neurodegeneration and CNS swelling affect tens of millions of people every year. While the symptoms can sometimes be managed with limited success, there is still no medicine to prevent the root cause.

Normal Brain Brain swelling Neurodegeneration



FLOWCODE is designed to map the CNS plumbing system in detail, identify the valves that control it and study how these valves are affected after injury or as we age. This will allow us to develop medicines that target, at their source, CNS swelling and neurodegeneration.

FLOWCODE will model CNS fluid flow as an engineered clearance network, inspired by the success of treating the cardiovascular system, in the last century, as a network of pipes. By understanding that blockages in these pipes (the blood vessels) led to heart attacks and strokes, scientists and clinicians worked together to develop medicines (statins) that could prevent those blockages from happening. Widespread use of statins has reduced heart attacks by almost a third and added healthy years to lifespan. *FLOWCODE's goal is to apply this thinking to the brain and define the CNS plumbing system.* This will provide a framework for halting CNS swelling, delaying the onset of neurodegeneration and adding quality of life to our later years.

2. HOW IS IT DONE TODAY, AND WHAT ARE THE LIMITS OF CURRENT PRACTICE?

Worldwide, over 55 million people currently live with dementia, which is just one form of neurodegeneration. There is no cure. As global lifespan continues to increase, this number is expected to triple by 2050. Dementia is one of the major causes of disability and dependency amongst older adults. In 2019, dementia cost the global economy $1.3 trillion. It also comes at a very personal cost, with family members providing an average of five hours of unpaid care per day.

A persistent lack of understanding of the pathways that lead to dementia has resulted in limited pharmaceutical drug discovery pipelines. After more than 4,000 clinical trials, there are still no

medicines that can prevent dementia. Symptom management using anti-amyloid antibodies has shown limited success and, unfortunately, causes brain swelling in some Alzheimer's patients, reflecting the complexity of the disease.

While dementia is one scourge, an additional 50 million people suffer traumatic brain injuries (TBI) each year, 12 million suffer a stroke and 15 million live with spinal cord injuries (SCI). Swelling of the brain or spinal cord – known as CNS oedema – is currently managed by controlling symptoms because, again, no medicines are available that can treat the root cause. Symptom management includes induced coma or high-risk surgery. In the case of brain swelling, decompressive craniectomy is used to remove part of the skull to relieve pressure. This procedure has a mortality rate of 20%, while 28% of patients will experience moderate-to-severe disability. After more than 360 TBI clinical trials, there are still no medicines that prevent brain swelling.

The unmet clinical need for medicines that target the underlying neurobiology of neurodegeneration and CNS swelling and improve both short- and long-term outcomes is clear. Indeed, unresolved CNS swelling is itself a risk factor for neurodegeneration. Targeting the CNS plumbing system offers a new approach to the development of therapies for these patients, who currently have very limited options.

3. WHAT IS NEW IN FLOWCODE'S APPROACH AND WILL IT BE SUCCESSFUL?

Disruptions in the normal functioning of the CNS plumbing system lead to CNS swelling following acute injury and cause neurodegeneration as we age. Medicines that can alleviate this disrupted flow will be transformative for tens of millions of patients. The FLOWCODE approach is to identify the protein 'valves' that control the CNS plumbing system and determine what causes the valves to open and close. We already know that after injury, opening of a specific valve (a protein called aquaporin-4) causes water to rush into brain cells at the site of injury and cause swelling. Work in my own team has demonstrated that targeting aquaporin-4 with the licenced anti-psychotic medicine, trifluoperazine, prevents this from happening and reduces CNS swelling in pre-clinical models.

An immediate goal for FLOWCODE is therefore to run a repurposing clinical trial in CNS oedema patients. Drug repurposing is the process of identifying new therapeutic uses for licenced medicines. The market for repurposed drugs was valued at $24.4 billion in 2015 and is predicted to be $35 billion by 2027. Compared to developing new medicines, repurposing has shorter timelines and higher approval rates as the medicines have already been tested in humans. Repurposing trifluoperazine will provide decisive proof that the CNS plumbing model is actionable in people and will deliver a first-in-human therapy to reduce CNS swelling as a near-term, unambiguous output of FLOWCODE. This will derisk the future development of a daily pill that can open up the faulty valves that would otherwise cause a reduction of fluid flow if left untreated as we age. This 'statin-for-the-brain' will delay the onset of neurodegeneration by restoring the health of our CNS plumbing system as we sleep.

In order to achieve that goal, *we need to find and characterise all the valves in the CNS plumbing system* that work in concert with, or independent of, aquaporin-4. Our understanding of CNS fluid flow in living brains is only 15 years old and is incomplete. Data describing the molecular changes accompanying CNS flow throughout the sleep/wake cycle in healthy brains, following injury or in neurodegeneration are incomplete and need consolidating and validating. Comprehensive mathematical models are additionally required that can express system dynamics using technologies that only now allow for the visualization of CNS fluid flow in humans.

Using AI tools (such as Edison) and computational approaches not available even 12 months ago, the scientific literature (especially on the anatomy of CNS fluid flow) and existing databases (such as the BRAIN Initiative, the Human Brain Project and the UK Biobank) will be mined to create comprehensive, annotated maps of the mouse and human CNS fluid flow pathways, correlating local flow rates with the local abundance of proteins to identify these valves. Where necessary, experimental validation will be done in the laboratory.

FLOWCODE's maps will be made accessible to the scientific community via a fully searchable online platform that is validated and open to all. As such, FLOWCODE will address a significant knowledge gap, transform our understanding of CNS fluid flow and open up many new lines of research. It will create foundations that others can build upon, cascading the opportunity for drug discovery to as wide a userbase as possible. A key goal will be pinpointing the location of all valves within the plumbing system, as they are the future drug targets for the treatment of CNS swelling and the prevention of neurodegeneration.

4. WHO CARES? WHAT DIFFERENCE WILL IT MAKE?

FLOWCODE will deliver a brand-new therapeutic framework to treat CNS swelling and delay the onset of neurodegeneration. A drug that targets the root cause of CNS oedema would offer faster recoveries, fewer complications and better long-term outcomes for tens of millions of patients and their families every year. These conditions currently account for tens of billions of dollars in annual healthcare costs globally. CNS waste clearance is a key player in the onset of neurodegeneration, yet until now we have lacked a molecular handle to manipulate it. FLOWCODE opens the door to a new class of medicines that could preserve CNS waste clearance function as we age, delaying or even preventing the onset of Alzheimer's, Parkinson's and other forms of neurodegeneration, reducing the global economic burden, which is expected to exceed $3 trillion annually by 2030.

5. WHAT ARE THE RISKS?

The main risks lie in the complexity and variability of CNS fluid dynamics. However, the identification of statins as modulators of the cardiovascular system tells us that a 'plumbing system' approach can produce life-changing medicines from complexity. There is also a risk that integrating multi-scale data will be technically demanding. To mitigate these risks, FLOWCODE will validate models against both experimental datasets and the outcomes of the clinical trial, creating a feedback loop between all elements of the programme design. However, the most significant strategic risk is that FLOWCODE is not funded at the scale required. It is too large and integrative for conventional academic funders, yet too early for venture capital even though its financial and therapeutic impact could be extremely significant.

6. HOW MUCH WILL IT COST?

Total Budget: £25M over 5 years to create FLOWCODE, a virtual institute, that will curate, generate and host dynamic CNS plumbing maps in health, injury and neurodegeneration. A repurposing clinical trial will demonstrate CNS plumbing is actionable in humans.

- Clinical Trial and Patient Studies (£8M). Trial conduct, imaging, patient follow-up.
- Pathway Mapping and Proteomics (£10M). AI infrastructure, proteomics services, validation.
- Data Science (£4.5M). Computational infrastructure, physicist/mathematician FTEs.
- Integration and Platform (£2M). Online platform development, data management, IP strategy.
- Programme Management (£0.5M). Coordination, reporting, stakeholder engagement.

7. HOW LONG WILL IT TAKE?

Phase	*Duration*	*Focus*	*Key Milestone*
Stage 1: Foundation	Months 0-24	Data mapping + planning for a repurposing clinical trial	FLOWCODE launches Clinical trial receives approval
Stage 2: Validation	Months 24-48	Model refinement + clinical trial execution	Trial completes enrolment Model validated against experimental datasets
Stage 3: Integration	Months 18-60	Full FLOWCODE integration + pharma partnerships + transition planning	Trial results published Drug candidates prioritised

8. WHAT ARE THE MID-TERM AND FINAL "EXAMS" TO CHECK FOR SUCCESS?

- FLOWCODE's repurposing clinical trial demonstrates a reduction in admission to neurosurgery by >40% compared with standard of care.
- FLOWCODE database maps >500 CNS fluid flow pathway proteins in mouse and human with AlphaFold2 structures and druggability scores.
- Spatial proteomics validates ≥5 novel regulatory mechanisms controlling CNS fluid flow.

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