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Bio-inspired nanofibres: Weaving biological tissue with nanomedicine to repair brains

By using biologically-inspired nanofibres as an innovative form of 'scaffolding', scientists are learning how to help the brain to repair tissue by itself, hopefully resulting in potentially far less invasive, life-saving treatments for traumatic brain injuries and tumours.

Imagine you get your test results from your healthcare provider after a consultation and you are told that you have a growth in the region of the motor cortex in the frontal lobe of your brain. If left unattended, it will grow and affect your ability to perform fine motor movements (e.g., the ability to move your hands, fingers, and wrists). The good news is that the growth can be removed. The bad news is that removing the growth may also result in exactly the same fate for your fine motor abilities due to possible impairment from surgical injury.

Do you risk the complication of losing motor function? Or do you leave the growth, let it slowly grow, and accept your fate? What do you choose? Are these the only options? These are the dilemmas that healthcare practitioners and patients are routinely confronted with in hospitals daily and globally.

In South Africa, brain trauma is a leading cause of death in children and young adults; furthermore, the incidence of traumatic brain injury (TBI) is 150-170/100 000, a higher value compared to the rest of the world at 106/100 000. There is yet to be a solution to regenerating brain tissue that exhibits consummate results of an effective clinical standard. Critical care resources to manage TBI for optimal outcomes in South Africa are also generally lacking.

Brains are tricky

Fortunately, there is an opportunity to apply pharmaceutical knowledge to design novel interventions in this regard. An aspect of our research work at the Wits Advanced Drug Delivery Platform (WADDP) research unit is concerned with fabricating scaffolds for application as tissue-mimetic implants that provide pro-regenerative platforms to support healing and tissue regrowth in difficult to heal tissues like the brain.

So what do we mean by 'difficult to heal' tissue, such as the brain? To create a solution, we must understand the problem well. There are several factors contributing to the challenge. When something penetrates the brain (e.g. surgical removal of a growth), a cavity forms which disrupts connections and creates a distance between neurons and supporting structures. The second challenge is the hostile environment created at the injury site from the formation of a glial scar, accumulation of inhibitory molecules, and the secretion of free radicals via the blood-brain barrier (BBB) breach resulting in secondary injury. This response is a double-edged sword.

On the one hand, this is a necessary response to injury; the brain forms this glial scar to protect the surrounding healthy tissue from secondary damage. However, this is

at the cost of regenerative capacity because surrounding cells cannot survive the hostile environment nor penetrate the scar tissue to reconnect with neurons on the other side. Reconnection of neural networks is essential to keep the communication flowing so that you can communicate to your brain that your hand is on fire, and your brain can communicate back to your hand to move out of the fire!

Clever scaffold-building

To support the reconnection, we use tissue-mimetic biomaterial scaffolds. A biomaterial is a material that can interact with biological systems and influence cells to behave in a certain way. Hence the name "bio" and "material". These materials can be in the form of synthetic, natural polymers or a combination thereof. An example of a polymer used for biomedical applications is gelatin; as you know, gelatin is also used to make candy and Jelly!

Polymers are selected based on processability into the scaffold designs we want and material closeness to that of the native extracellular matrix (ECM), the home of the cell. A scaffold, just like the scaffolding you would encounter at construction sites, functions as a temporary 3D structure providing support and a 'bridge' at the cavity site created after the healthcare provider removes the growth to help the cells cross and reconnect to communicate for tissue continuity.

A tissue-mimetic biomaterial scaffold should be designed to "mimic" the target tissue-building requirement needs. When we talk about tissue building requirements, we talk about the ECM, the home of the cell. The important thing to note is that the ECM of each tissue has a unique architecture. The brain has been previously described as resembling foam, once described as an "intricate interwoven fibre meshwork of collagen and elastic fibres embedded in a highly hydrated gel-like material of glycosaminoglycans, proteoglycans, and glycoproteins". Examples of tissue-mimetic three-dimensional biomaterials scaffolds synthesised at WADDP include but are not limited to hydrogels, cryogels, nanofibres and the combination thereof (Figure 1).

Let's zone in on nanofibres as examples of biologically inspired scaffolds and ways they can be used as a strategy to weave biological tissue with nanomedicine to solve our dilemma with the growth in the brain.

Nanofibres are defined by their name. The 'fibre' portion refers to the threadlike shape of the fibres (Figure 2). The 'nano' portion refers to the size of the nanofibres. Nano size refers to a size that is 1 billionth of a meter. This means that the nanofibres are so tiny that you will never be able to see one with the naked eye. What you see instead is a 'nanofibre mat', which is simply hundreds and thousands of single intertwining nanofibres overlaid on top of each other (Figure 2b). Compared to everyday objects like the diameter of the thin silk spun from a spider that is already barely visible to the naked eye (approximately 3 500 nm), nanofibres are approximately 300 nm, making them 14 times smaller than a spider's silk thread. Therefore, the actual image of a nanofibre can only be seen using an electron microscope (Figure 2c).

The female *Nephila clavipes* spider (see main photo) has a spider web silk strand of a few micrometers (µm) thickness in this electron micrograph (Figure 2a). Nanofibres are electrospun at the WADDP research unit with Figure 2b being an electrospun nanofibre mat and Figure 2c a scanning electron micrograph of nanofibres, at the same scale bar = 1µm. They are tiny!

Despite their small size, nanofibres have a very big role in society, with a wide range of evolving applications in healthcare, such as gene and drug delivery, cell therapy, cancer therapy, tissue engineering, regenerative medicine and use as biosensors. Figure 3 depicts the conceptual application of nanofibres as brain implantable tissue-

Figure 1: Examples of biomaterial scaffolds fabricated at WADDP

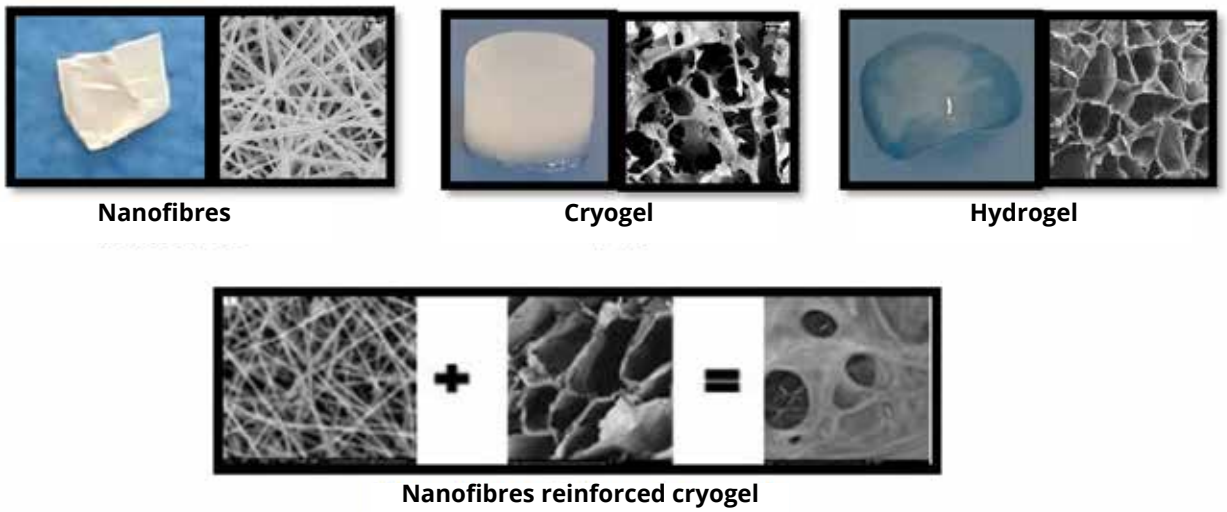
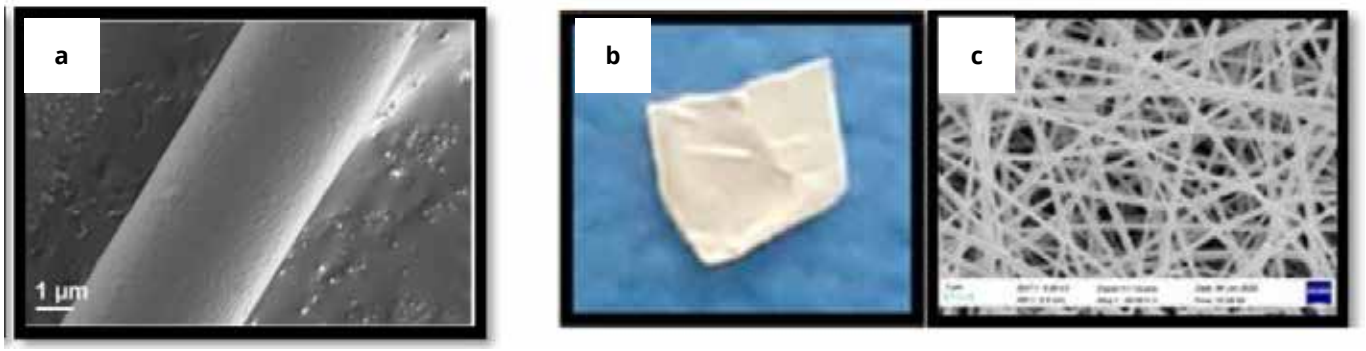


Figure 2: Explaining electrospun nanofibres



mimetic scaffolds able to be loaded with a drug to be delivered to the brain.

Loading drugs into nanofibres is achievable because of the ease and flexibility of the electrospinning method used to fabricate nanofibres. Moreover, nanofibres present a nanoscale architecture closely resembling the aforementioned native ECM structure of tissues like the brain. They also present with a very large surface area to volume ratio, which allows more space for presenting topographical cues to support the attachment of neural cells, their guided migration and the extension of their processes and axons across the distance of the cavity site to help with the desired tissue reconnection. The ability to guide cell growth is a major advantage of nanofibres' structure to ensure neurons extend towards each other instead of 'circling' around aimlessly.

Revisiting our case scenario, could nanofibres be a viable intervention in the future to minimise the risk of losing motor function after the tumour is removed? You decide! Cutting-edge breakthrough research, passion and curiosity are key to developing novel actionable solutions to multifaceted healthcare problems.

This requires looking at materials and delivery systems with an openness to their potential for application and problem solving (e.g. application of nanofibres as implants, wound dressings, nanofibrous gels, drug delivery systems and biosensors). This has been a small glimpse into the world of WADDP. If you are curious and need more helpful resources on subjects like nanofibres and other drug delivery systems, get in touch or visit https://www.wits.ac.za/waddp/.

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Figure 3: A conceptual diagram of nanofibres as brain implantable drug-loaded tissue-mimetic scaffolds (left) and the NanoSpinner24 machine used at the WADDP research unit for electrospinning of nanofibres (right)