

Undoing the Straitjacket

Sandra explodes into motion like a sprinter off the blocks, seizing the bucket of ice cubes and swiftly upending it over herself. Her expression turns from anticipation to paralysed terror. Muscles taut as steel cables, body rocking stiffly as if cement fills her joints. In shivering shock, she awaits normality. As her body temp normalises, her passion follows. She screams and leaps about the garden as if tailed by a swarm of hornets.

Her father, Charles, has positioned his wheelchair for perfect viewing of this surreal sight. Guffawing and applauding, he has no need to empty a bucket of ice over himself to simulate her sensation. The Ice Bucket Challenge was rather poignant, in that regard. But unlike his daughter, Charles' racking stiffness won't fade. It only heralds the beginning of a dark descent...

Motor Neurone Disease (MND) is a devastating neurodegenerative disorder that kills 4 of every 5 patients within 5 years of diagnosis. Since first described by neurologist Jean-Martin Charcot in 1874, there has been no significant breakthrough – certainly no cure. Only Riluzole, the modifying therapy prolonging survival by months at most....

Its invisible straitjacket tightens at breakneck pace, whisking you on a frightening journey of physical decline. You lose the ability to move your arms and legs, speak, swallow and eventually, breathe altogether.

As I test the power in Charles' arms during one of our consults, I tell Charles with confidence that study into MND has never been stronger. "One day," I say, "our nervous system won't be unrepairable." His wry look echoes the less hopeful of the medical community. To change that expression means everything to me.

The brain is so complex that we cannot run tests on it as simply as on other organs. Such an approach would require a brain matter biopsy or close monitoring of specific drug effects via regular scanning. And neither of these are what you'd call 'comfortable' procedures.

"Rather than extract nerve cells from patients' brains," I tell Charles, "we take skin cells and reprogram them back in time – to default generic cells like those in embryos – then turn them into specialised brain cells like neurons and astrocytes." Stem cell reprogramming was pioneered in 2006 by Shinya Yamanaka with his renowned and rather fluffy lab assistant: Dolly, the world's most famous sheep. Sorry Shaun, we still love you...

“I use these cells to create ‘disease in a dish’ models recapitulating MND’s key aspects, to better understand its biology.” Understanding is the first step to treatment, in which we compare behaviour of diseased and healthy cells to develop a fantastic approach to drug discovery. Like anything, a decent metaphor brings the narrative to life.

“Listened to any good music recently?” I ask at our next consult, knowing Charles loves a quality composition. There’s a Mozart piano quartet he holds dear, a beautiful, intimate recording by a Scottish quartet. He almost drifts off as he recalls the soothing music from his vintage hi-fi. The stage – and soundtrack, no less – for my story is set.

“The neurons that form the brain’s building blocks don’t live in isolation. They’re surrounded by three other cell types called *glia* (from the Greek meaning ‘glue’), each vital for neuron prosperity. In harmony, these four cell types create an extraordinary symphony of electrical activity.” My narrative rallies, Charles smiles.

“This electrical activity allows us to emote, remember, move – feel every sensation there is. But if just one cell misbehaves, the tune falls flat. And if the first to decline is a neuron, MND rears its head ...”

Charles nods once more, visualising the quartet of brain cells playing his beloved Mozart, before admitting he’s never heard of glia cells. They’ve been long-neglected in the field, with most emphasis upon the study of neurons.

“Though the piano is the star, the performance is incomplete without supporting players. The neurons, likewise, rely on the glia.”

I tell Charles my research focuses on one glia cell: the astrocyte. If the human brain were the night sky, astrocytes would be the stars twinkling with brightness and vitality. They regulate neurons and their environment by providing nutrients, clearing waste, and repairing brain and spinal cord damage. “Let me guess... They look like stars?”

I point to an image on my office wall. Their nomenclature receives Charles’ nod of approval. Humble questions like these, from patients like Charles, fuel my search for a cure.

In simple words carrying deep responsibility, I explain that my goal is to find medicines that not only halt brain degeneration but actively reverse it.

“Like one day I’ll be able to play my piano again, you mean?”

I speak on behalf of the entire world's MND researchers – an especially ambitious bunch of boffins – that we will one day find a way for those suffering from MND to live longer, enjoy life and their families.

“And when will that be?” asks Charles with trademark cheek and a check of his watch. I wouldn't lie to him – I have no answer. But the intent is there, lining each petri dish in which I poke about, beckoning the brave face I don daily for the assurance of those like Charles...

Right now, I compare healthy astrocytes with those of patients with MND, which carry the C9orf72 mutation. To date, over 25 MND-related genes have been discovered, and C9orf72 seems the most common genetic cause. I grow healthy and MND astrocytes with human motor neurons and examine their effect on neuron health and architecture.

So far, I've found motor neurons mixed with errant astrocytes are much smaller and less branched. Is it due to direct contact of motor neurons with MND astrocytes, a consequence of toxic substances released by astrocytes, or both? By identifying genes, proteins and pathways affected, we may one day banish this cruel monster.

Charles is positioning his wheelchair to depart when my phone rings. “Dvorak's Humoresque,” he muses. “Not bad at all.”

Like the Czech folk composer's ponderous pieces, an undying sense of direction buoys our research. With ongoing support from institutions like the MRC, and the awe-inspiring resolve of our patients, a far light glimmers. The payoff may not be definable in this instant, yet our progress toward it will not halt.

This is not just history in the making – to visualise a better future and work towards it is one of humanity's most fundamental ideals. Only 15 years ago, our work was considered impossible. In another 15, perhaps a cure is plausible. One day, MND patients will take showers, tie shoelaces, and hug their loved ones without assistance.

Now that's music to my ears.