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WINNER

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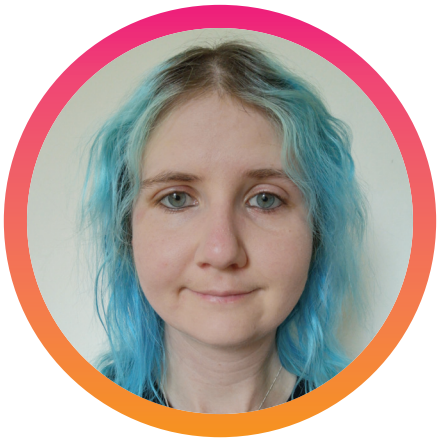


CURING THE INCURABLE: TEACHING AN OLD DRUG NEW TRICKS TO FIGHT OVARIAN CANCER

She sits in the small consulting room once again, waiting to hear the news of her latest scan. It has been a difficult journey since the last time she sat in this chair, before her most recent round of treatment began. Over a month of exhaustion, vomiting, soreness, sleepless nights and the inevitable hair loss. But this time, the chemotherapy has not been successful. After all the side effects, all the pain that she has endured, her tumour is still growing, a dark mass on her ovary. Where does she go from here? What can she do when the treatment she's pinned all her hopes on just stops working?

This situation is all too common for women with high grade serous ovarian cancer (HGSOC), a devastating form of ovarian cancer. Only 35% survive longer than five years following their diagnosis. While chemotherapy and surgery are highly effective at initially shrinking tumours, the cancer continues to fight back. Over time the tumour changes, with cells that survive treatment prevailing and replicating, passing on the protective traits that give them that survival edge. The tumour becomes completely resistant to chemotherapy, and no barrier remains to stop it from growing out of control and overwhelming the body.

However, there are groups of patients whose cancers are much more sensitive to chemotherapy treatment than others, who can be completely cured by chemotherapy.

One key to this is DNA repair proteins, the tools that all cells use to protect their DNA from damage. Think of this DNA as the instruction manual for a cell, detailing how to build all the proteins the cell requires to live and carry out different functions. Cancer cells often have defective DNA repair proteins, as this allows them to adapt and grow rapidly. Strange as it may sound, this can be a good thing from our perspective! Chemotherapy kills cancer cells by attacking their DNA, and those which lack DNA repair proteins essentially forgot to bring a first aid kit – they cannot fix themselves up and keep going. This means that the chemotherapy can completely kill off the cancer, so the patient will survive. This reveals gaps in the armour of this cancer, which we can exploit to help the women who need it most.

No two cancers are quite the same, even within a specific type like HGSOC. Some have completely functional DNA repair proteins. Some have defective proteins initially but can adapt and fix these. Others can make excessive amounts of the proteins to combat the effects of chemotherapy and survive. I hope that by learning what happens to these proteins as a cancer cell becomes resistant to chemotherapy, I can make new drugs to prevent the crucial DNA repair proteins from functioning, which will enable the chemotherapy to kill cancer cells more effectively.

The first question that I asked was which, if any, of these proteins are actually important for the way HGSOC reacts to chemotherapy. I used cells taken from HGSOC patient tumours and adapted to grow easily in the lab, called cell lines, which have similar properties to an actual tumour in a patient. By using cell lines taken from a selection of patient tumours, scientists can build up a picture of the similarities and differences between patient tumours. I started by assessing the growth of various cell lines when treated with a drug called Carboplatin, the standard chemotherapy used to treat HGSOC. The slower the cells grow, the more effective it is as a treatment. I found that there was a lot of variation in sensitivity to Carboplatin between the different cell lines – unsurprising really since one of the main challenges in cancer research is how many differences there are between individual's tumours, and even between different parts of the same tumour.

Next, I set out to find the reason for these differences, looking for changes in the DNA repair proteins. I studied a database of ovarian cancer patients looking for clues on what could be going on and found that it is common for the tumour cells to produce either abnormally high or low amounts of certain DNA repair proteins. So, I decided to measure the amount of repair proteins produced by my cell lines. I found that in the cell line that was most sensitive to chemotherapy, one of these repair proteins was almost entirely missing! This is a really good indicator that this protein could be an important factor behind repairing the damage caused by chemotherapy.

So, I had identified a protein potentially involved in chemotherapy effectiveness. What next? I wanted to confirm that this protein acts in the way I suspected within the cancer cells. I blocked the cell lines from producing the protein I was interested in, and again looked to see how sensitive to chemotherapy the cancer cells were. This confirmed my initial suspicions – removing the protein made the cancer cells much more susceptible to chemotherapy!

As I am only in my first year of working on this project, there is still much to be done, but this is an exciting starting point. I certainly find it very exciting! I plan to study the mechanism used by these cancer cells to alter the amount of this repair protein, and see how smart the cancer cells are – are they cheating the chemotherapy by producing more of this protein to prevent the cells from being killed? Does this result in a chemotherapy resistant tumour? Most importantly, I would like to identify patients whose cancers have high levels of this repair protein, for whom conventional chemotherapy might be less effective, and focus on how I can help them. To tackle this problem, I would like to test drugs that block this protein from carrying out DNA damage repair, leaving the cancer powerless, unable to repair the damage inflicted by chemotherapy. My dream is that one day this will help more women to leave that consulting room feeling victorious, having beaten the odds, and able to shut the door for good on their way out.

RUNNER-UP

JULIA WCISLO

University of Dundee

THE GAME OF HIDE-AND-SEEK

Today is a big day. Today, after months of hard work, trial and error and several trips to the lab in my pyjamas during weekends, I will finally find out if I win the game of hide-and-seek. However, this isn't a typical game as I don't play it with my friends or family. I play it with deadly parasites.

For my PhD, I'm working on a parasite called Trypanosoma cruzi (T. cruzi). T. cruzi causes Chagas disease, one of the deadliest, tropical diseases in Latin America with around 8 million infected and over 14,000 deaths a year. If caught early, the disease can be diagnosed with a simple blood test. Unfortunately, Chagas is often symptom-free at this stage, so most people don't even realise that they're infected. As time passes, T. cruzi disappears from the blood and hides in various cells and tissues, often for 20-30 years before serious cardiac and digestive problems start to appear. By then, both diagnosis and treatment become a serious challenge.

Many researchers believe that *T. cruzi* hiding in cells and tissues makes it difficult for the drugs to reach the parasites and is, in fact, the cause of frequent treatment failures. To explore this theory, I'm trying to find exactly where parasites remain in those late stages of the disease after the drug treatment has been administered. This is where I enter the game of hide-and-seek.

In my research, I use parasites "tagged" with a fluorescent protein, which means that they emit a bright green light when microscopic light is shone at them. You could call it cheating, but considering their impact, I don't mind playing dirty.

Initially, the parasites had to be grown in a bottle. This involves keeping them at the correct temperature and immersed in a specialised liquid called media, filled with essential nutrients that allow them to multiply. For most parasites, the conditions must be ideal to survive, but *T. cruzi* isn't like most parasites. To prove how tough they are, I once left them for two weeks without any nutrients. When I examined the flask, there they were, wiggling their 20µm-long bodies as if nothing had happened. I must admit I have grown rather fond of my tough, microscopic "friends" and often treat them as a lot more than the parasitic killers they are. I know that asking the parasites whether the incubator is cosy enough isn't exactly normal, but before you call me crazy, you should know that some of my co-workers call them "their babies", so I'm definitely on the saner end of the spectrum.

After weeks of culturing, the parasites were used to infect our animal model – mice. Then we waited for *T. cruzi* to do what they're best at – establish the infection and hide. After some time, we harvested the infected organs for tissue clearing.

The organs had to be cleared for a simple reason: they are not transparent. Fluorescent parasites have to be exposed to a microscopic light to be visible, and you can't shine a light all the way through a thick tissue sample.

The majority of biological tissues aren't transparent because every component of the tissue has a different refractive index (RI), which determines how much the path of light is bent or refracted. Take clouds as an example.

They're made out of water, which is transparent, but you can still see clouds, right? This is because the water droplets that make up the cloud have a different RI from the surrounding air. So as the light passes through a cloud, it's scattered, which allows us to actually see the cloud. If you were to replace the air in the cloud with a gas that has the same RI as water, the cloud would become completely transparent.

Tissue clearing works in a very similar way. Biological tissues contain proteins, lipids and water, each with a different RI. Tissue clearing involves a series of chemical steps, which aim to remove, replace and modify some of the tissue components resulting in all structures having the same RI and the organ becoming transparent. This way, light can easily pass through it and I can look for my green parasites even in the deepest areas of the sample. It's been a long process and today I am finally able to take my infected, transparent hearts and intestines to the microscopy facility.

Two colleagues and I sit in a darkened room, preparing the microscope. We put the samples in, start scanning and then...

"I found you...", I whisper, my eyes fill with tears while Erika starts to perform her victory dance. Michael who doesn't work with parasites doesn't share or understand our enthusiasm, although he clearly finds our unusual behaviour rather amusing. A few dim green dots (a small nest of parasites) are visible in the wall of the large intestine, sitting there, thinking they can hide from us. Not this time amigos! After so many months, I finally win.

Of course, my work doesn't finish there. Ahead of me are several more months of improving the method for other organs. Nonetheless, this is a great advance. Using tissue clearing is a completely novel approach that has great potential to make an impact in the field of parasite localisation. If I manage to optimise this method and publish results, I will reveal *T. cruzi* hideout spots, so then other scientists will be able to design new drugs with properties that allow them to penetrate these hideouts.

This game of hide-and-seek is worth playing. Current treatments for Chagas have been used for over 50 years and so far, there have been no advances in this area. Certainly not for lack of trying. Several compounds from many different labs, including ours, were designed but all failed to give full, sterile cure in the animal models. This only proves that there is a major lack of understanding of the parasite's underlying biology, and research into this basic knowledge is essential.

Obviously, there is no guarantee that the reason for drug failures depends solely on poor drug distribution to where *T. cruzi* hides. Recently, it was discovered that *T. cruzi* can temporarily enter a state in which their normal physical functions are stopped or slowed down, which potentially protects them from any treatment effects, but that is another game. What matters is that with each discovery we are one step closer. Hopefully one day, with the efforts of all researchers working on Chagas disease we will be able to tame this deadly condition. We're still far off, but today...today, I feel like a winner.

COMMENDED

MIRANDA BUCKLE

MRC Doctoral Training Partnership
University of Oxford

BABY, WHAT'S ON YOUR MIND?

"Is he in pain, doctor?"

I look down at the tiny baby lying in front of me. He weighed less than a take-away coffee when he was born prematurely. So early his skin was translucent, and his eyes were still fused shut. Too early even for fingerprints to have developed.

His father looks at me anxiously.

I am carefully checking that his son's eyes are developing well. That there are no signs of a serious eye condition called Retinopathy of Prematurity which can lead to irreversible blindness.

Unfortunately for the baby and his father, I think the eye check is painful.

I can't tell him for sure though, because there is still so much to be discovered about how premature babies experience the world.

Until the 1980s there was a misconception that newborn infants did not feel pain. It may sound unbelievable now, but major cardiac surgery used to be performed without anaesthesia on these tiny babies. Doctors thought that newborn infants couldn't tell the difference between a painful sensation and a gentle touch. So, they didn't use anaesthetic.

Parents had to campaign hard to change medical practice. Finally, in 1987 a clinical research trial successfully showed that infants who were given anaesthesia during surgery were much better off than those who endured the operation without anaesthesia. Their heart rate and breathing were more stable. They had lower levels of stress hormones. They developed fewer serious problems after the operation.

Pain in babies is now understood to be a serious issue. On average, premature infants face between 12 to 16 painful procedures per day while they are in intensive care. These babies may be hospitalised for several months. All that pain adds up.

Researchers have discovered that early life pain can affect brain development. Pain exposure even may influence the IQ a child achieves as it grows up.

But there is still a lot more to find out.

Knowing when a baby is in pain is more complicated than it might first seem. Of course, we can't ask babies how they feel. So, we have to use substitute measures that may reflect their experience. Are they crying? Is their heart racing? Is their oxygen level low?

However, substitute measures aren't perfect. Yes, a baby may cry from pain, but they also cry when they are hungry, tired or lonely. Or for no reason at all, as any new parent can attest!

Can we find a sure-fire way to detect when a baby is in pain?

Since pain is a sensation that comes from the brain, the answer may lie in decoding babies' brain waves. Brain activity in babies has been investigated over the past 15 years.

Researchers have discovered that babies' brain waves show a characteristic pattern of activity in the milliseconds after they experience a short, sharp pain – such as a blood test. This pain-related pattern can be detected even in fragile babies who are too ill or too tired to show outward signs of distress.

So, we can tell if a baby felt pain from a blood test. And we can tell if pain relief is effective. For example, local anaesthetic gel or gentle stroking both reduce babies' pain-related brain activity after a blood test. Good to know!

But what happens in babies' brains after more complicated painful procedures?

To answer this question, I used a technique called electroencephalography (known as EEG). EEG is a baby-friendly technique that uses sensors to record the baby's electrical brain activity. I studied babies' brain activity while they were having their eyes checked for Retinopathy of Prematurity.

I looked for differences in EEG recorded for several minutes before and after the eye check. Finding the differences required careful data processing and complex computer analysis of the interplay between different brain waves.

Brain waves are named after Greek letters: there are delta, theta, alpha, beta and gamma waves. If brain wave frequencies were musical notes, delta waves would be low notes, and gamma waves would be high notes. When premature babies are born, most of the brain activity "music" is composed of low notes. As babies' brains develop, the music becomes more complicated and varied.

So, what have I discovered?

I found there is a characteristic change in premature babies' brain activity after the eye check. Higher frequency brain waves are increased for several minutes.

But can we be sure that this change in babies' brain activity is pain-related? The eye check involves holding the eye open and shining a bright light inside. Maybe the changes are related to stress?

To look into this, I recorded babies' brain activity while they had their nappies changed! Nappy change takes about the same time as an eye check. Premature babies can show signs of stress during a nappy change such as crying or increased heart rate. But of course, changing a nappy is not considered to be painful.

I found that nappy change did not cause the same characteristic increase in premature babies' brain waves.

So, the changes I observed after the eye check are related to pain rather than stress.

Investigating pain-related changes in premature babies' brain activity after complex clinical procedures has never been done in this way before, so this research is very exciting.

What does this mean for my patients and their parents?

My work gives us a better etanding of how painful clinical procedures influence babies' brain activity. We can combine this information with what we know about how pain affects babies' behaviour and vital signs. This will help us to better detect pain in babies.

The next step is treatment. Can we find pain-relief strategies that reduce pain-related brain activity after an eye check or another painful procedure? More research is needed to answer this critical question.

Then when an anxious father asks me whether his newborn baby is in pain, I will be sure of the answer. And more importantly, I will be able to offer an effective treatment. In doing so, I will be able to give every premature baby the best chance for healthy brain development.

COMMENDED

MARIA STAVROU

University of Edinburgh

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 four of every five patients within five 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 reprograming 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.

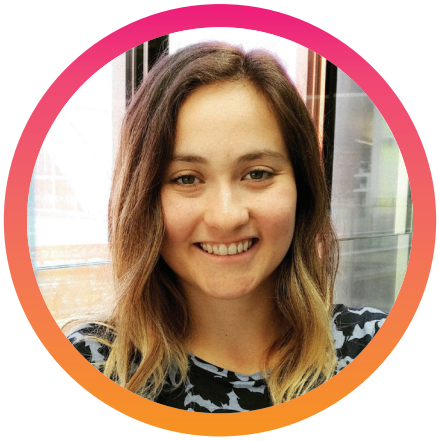
This is not just history in the making – to visualise a better future and work towards it is one of humanity's most fundamental ideals. Only 15 years ago, our work was considered impossible. In another 15, perhaps a cure is plausible. One day, MND patients will take showers, tie shoelaces, and hug their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

Now that's music to my ears.

COMMENDED

FERNANDA TEIXEIRA SUBTIL

Francis Crick Institute



FROM THE PALACE TO THE FAVELA

"So what? I am Messiah but I can't do miracles", said Brazilian President Jair Messias Bolsonaro when asked about the 10,000 deaths in the country due to the COVID-19 pandemic. This number is now 14 times higher. You might be shocked by his neglect; how can someone, especially in his position, disregard so many lives? As appalling as it may be, he is not the only one. In fact, all of us have been overlooking the pressing need to prevent, treat and cure several infectious diseases that impact our world.

In Brazil, the first COVID-19 cases were of those infected during their trips to Europe, a type of holiday that few can afford. In contrast, other diseases that don't usually affect middle and upper-class individuals, called neglected diseases, have been tormenting our society for hundreds of years, but most people seem to have forgotten them.

Over the last six years I have been studying tuberculosis (TB), one of these recognised neglected diseases. On multiple occasions I have had to explain to my friends and family why I chose to study a "disease from the past". I have now gotten used to seeing the shock on their faces when I tell them that over 1.5 million people died from TB in 2018, higher than the number of fatalities caused by COVID-19 so far. Most of them do not know that TB is highly endemic and a significant public health issue in Brazil, where I am from. Now that I moved to the UK the same situation occurs, people are surprised to know that London has been called, "European Capital of TB" by The Guardian. This unfortunate nickname comes from the fact that 40% of the 5,000 TB cases reported in England are from London.

As years have passed, TB has lost all the attention of the media and of most of the world's population. Called *mal du siècle* (illness of the century) in the 1800s, at a time when it affected anyone and everyone, killing even the most respectable members of society, it has now become a disease of the poor or incarcerated — those belonging to the periphery of society. It is a disease disregarded by our leaders and forgotten by the elite. Unlike COVID-19, TB tends to affect individuals in vulnerable situations where there is low sanitation and poor nutrition.

The 19th century romanticism portrayed the different facets of tuberculosis at that time. Puccini's *La Boheme* was the first opera I ever saw. I was touched not only by the beauty of the music, but also by the social problems that resonate with the circumstances we face today. The protagonists live in poverty and marginality. The heroine, Mimi, dies of tuberculosis without any medical intervention. Sadly, Mimi's lover abandons her, probably for fear of infection, as tuberculosis, like COVID-19, is a respiratory disease transmitted through coughing of an infected individual.

Since the late 19th century, several scientific developments for treating and preventing TB came to be. Not only do

we have a vaccine that can prevent the most severe TB forms in children, but we also have a plethora of antibiotics that can kill *Mycobacterium tuberculosis*, the bacteria that causes the disease.

TB treatment involves the use of a combination of four different oral antibiotics over the course of six months. While six months may sound like a long time, this is the best-case scenario. In the past few years, there have been an increasing number of infections caused by drug-resistant *M. tuberculosis,* where the usual treatment is no longer effective. In these cases, alternative antibiotics are used. This regimen involves around six drugs, mostly injectable, presenting more toxic effects. As if this weren't enough, cure can take up two years. COVID-19 has been affecting us for nine months and most people are shocked that we don't yet have an effective treatment or a vaccine, but we have been dealing with TB for over a century with treatments that are far from satisfactory and a vaccine that is only partially effective – no one talks about it.

When I first started researching TB, I focused on finding new antibiotics to treat it, but then I realised that the bacterium always finds a way to evolve and resist antibiotic action. *Mycobacterium tuberculosis* is inherently resistant to a wide range of antibiotics because it grows very slowly and surrounds itself with a thick wall – drugs just can't get in. Additionally, TB already has intrinsic inactivation mechanisms for some drugs. For instance, meropenem is a widely used antibiotic, but *M. tuberculosis* produces a protein that is able to destroy it. Thankfully, scientists have discovered a molecule called clavulanate that, in turn, inactivates this meropenem-degrading protein, subduing the bacterium completely. I find fascinating, the fact, that tuberculosis and many other resistant bacterial infections can now be treated with this clavulanate-meropenem combination.

After this realisation, I redirected my focus to search for unknown modes of antibiotic resistance. Much like we are learning from other coronaviruses to better understand this new virus responsible for the pandemic, I am sweeping all microorganisms closely related to *M. tuberculosis*, a group called mycobacteria, to find proteins that can modify antibiotics, instead of focusing only in *M. tuberculosis*. My comprehensive search has encompassed proteins known to exist in other microorganisms, and proteins that have never been described before, some of them capable of degrading even modern synthetic antibiotics. These mechanisms are already present in nature and have been for billions of years, and yet they work against human-made compounds.

By unravelling existing mechanisms of antibiotic resistance, we can design molecules able to neutralise them so that the antibiotic can take effect. Wouldn't it be remarkable to have another story like meropenem's?

Since we already have a range of antibiotics available, we must find ways to make them work against resistant bacteria. This repurposing strategy also has a very important and appealing advantage compared to finding new drugs, as a new medication takes about 13 years from its discovery to the market, so repurposing approved drugs is a much faster and cheaper approach.

TB is only one of many neglected bacterial diseases that can be tackled using this cost effective and fast strategy. By studying resistance mechanisms that are present in nature, we can potentially develop novel "resistance-proof" antibiotics or combinations that will ultimately help us cure nearly-incurable diseases. Some might call this a miracle.

SHORTLISTED

KIRSTY BALACHANDRAN

Imperial College London

PROGESTERONE: AN UNTAPPED RESOURCE FOR TREATING BREAST CANCER?

Carol sits patiently as I pull up her scan results on the screen. Her husband holds her hand and absent-mindedly drums his fingers, betraying the nerves they both must feel. Today is the day they find out if the treatment Carol has been receiving for breast cancer is working. When we discovered earlier in the year that the cancer had spread to her liver, we discussed that unfortunately the cancer was no longer curable. However, we were hopeful that this treatment would keep it under control and enable Carol to enjoy life relatively symptom-free for some time.

Carol's situation may sound familiar but with the sea of pink breast cancer charity adverts covering buses and billboards alike, it could be easy to wonder why breast cancer is such a big focus of research. After all, there is no shortage of other life-limiting diseases also without cures. Distinct from many of them, however, is the sheer number of people affected by breast cancer. As the most common cancer in women worldwide with over 2 million cases diagnosed globally each year, it's unsurprising that almost all of us have a "Carol" in our lives. If cancer is *The Emperor of all Maladies*, then surely breast cancer is the Empress.

For over three quarters of all patients, the hormone oestrogen is the fuel that drives the development and growth of breast cancer. In these patients, a protein in cancer cells called the 'oestrogen receptor' acts as a switch that "turns on" the cancer, making it grow in response to oestrogen. Hence many of the medications we use block the interaction between oestrogen and its receptor. Advanced cancer, which has spread outside the breast to bone, brain or beyond, eventually overcomes all these treatments, making it incurable. The 'progesterone receptor' and its hormone, progesterone, form another pairing but their significance in breast cancer is less clear. All patients with breast cancer are tested for both oestrogen and progesterone receptors as, interestingly, those that are positive for both respond much better to treatment.

The role of progesterone in breast cancer has long been debated. High doses of drugs that mimic the actions of progesterone and "activate" its receptor have been shown to be effective at treating breast cancer in clinical trials. These drugs are off-patent, costing just a few pence a day and are used for other conditions with minimal side effects. Conveniently, most are tablets, so don't need to be administered in hospitals. However, when these same drugs are given to relieve menopausal symptoms, they have also been reported to increase the risk of breast cancer. This paradox has pushed progesterone into the shadows when it comes to research and consideration of novel breast cancer treatments.

And so, as I check the progesterone receptor results for my patients, I often wonder about their real significance. What is the true effect of progesterone on breast cancer? Given

that every patient is already tested for the progesterone receptor and the drugs are cheap, safe and easy to take, are we missing a trick in not using them? I have taken these questions to the laboratory in the hope that studying breast cancer cells will provide some answers.

I am using breast cancer cells as experimental models of the cancers found in patients. By altering the conditions the cells are cultured in, I can replicate the environments of these cancers. For example, by removing all oestrogen, these cells are placed in a similar state to tumours in women treated with oestrogen-blocking therapies. I have manipulated the progesterone receptor in these cells to study how their behaviour changes, using natural and man-made progesterone treatments and even deactivating the progesterone receptor altogether. My early research shows that cells engineered to contain higher levels of the progesterone receptor are more susceptible to progesterone treatment. Excitingly, the growth of these cells is indeed reduced, particularly when treated with a man-made formulation that isn't used in menopause therapy.

In order to establish how progesterone is responsible for this decrease in cancer cell growth, I want to see how the activity of genes in these cells changes after treatment. With up to 25,000 genes in the human genome, it would take years to test each gene individually. Therefore, I use a technique called RNA sequencing, which determines the activity of all of these genes in just one experiment. I treat my breast cancer cells with drugs including oestrogen, progesterone and combinations of these, pack my precious samples in dry ice and entrust them to the international courier for transport to the sequencing facility.

A few months later, I receive a fairly unassuming hard drive in return. The raw data contains millions of pieces of sequencing information and requires processing. Once I have finished this, I have over four terabytes of data to analyse – the equivalent of 2,000 hours of high definition Netflix. I have learnt to code, writing programming scripts that extract the information I need. I then scour this for genes that become overactive following progesterone treatment and look for common characteristics and functions. My hope is that this will provide valuable insights into how progesterone is acting in these cells and will also identify other genes that can monitor how patients are responding to progesterone treatments – a warning system to reassure when the treatment is working and alert when it isn't.

A cure for advanced breast cancer would be revolutionary but until then, oncologists and researchers like me aim to add to the armoury of treatments that slow the cancer's progress. Used in sequence, they can offer good quality of life, sometimes for many years. Progesterone-based treatment is a tantalising addition to this. As drugs already exist, time-consuming drug development is unnecessary, meaning patients could benefit from these without delay. In low and middle-income countries which often have higher proportions of women with advanced breast cancer and reduced access to healthcare services, these inexpensive, readily accessible drugs could transform treatment options and survival rates.

Back in the clinic, it's good news for Carol today. Her current treatment remains effective. As we discuss this, we know that at some point in the future the cancer will evade this treatment and we will need to select an alternative. As Carol and her husband leave the room, I am hopeful that we will soon be able to include progesterone among those options, providing a safe, affordable and easily tolerated means of enabling all those affected by advanced breast cancer to live full and active lives for longer.

SHORTLISTED

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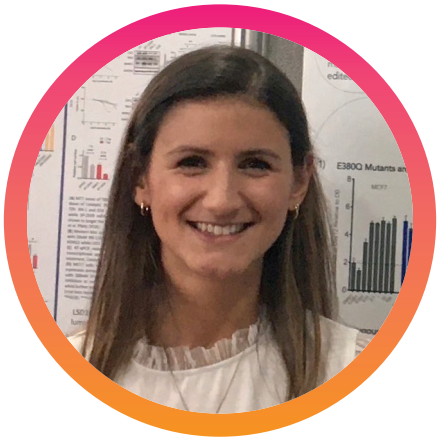

FINDING THE PATH OF LEAST RESISTANCE

It's the middle of the quarantine lockdown. The sun is shining stronger than in any other April on record, but the public are stuck indoors. Luckily, you have a beautiful garden, which you are now outside admiring. Something catches your eye – you spot a large cluster of weeds that have sprouted in your vegetable patch. Not to worry! Five minutes later you are armed with your gloves and gardening fork, ripping their roots from the soil.

What you don't know, however, is that beneath the soil, the roots of one weed were too strong to remove: a mutant, super-weed, if you will.

The following morning, you wake up and despair at the sight of your garden, now infested with super-weeds. You try to pull them out of the ground, but these mutant pests are resistant to your futile efforts. Didn't somebody once mention baking soda as a home remedy for weeds? After a light sprinkling of the soda, the weeds start to wilt – success! Relieved, you turn to tackle the rest of them, when the stark reality of your situation hits you. You look around and realise it is too late. Your garden is overwhelmed and beyond repair.

My PhD research is not about pesticides, nor am I a botanist. Rather, my work focuses on breast cancer, a debilitating disease affecting millions of women worldwide. Specifically, I study the most common type, called '*ER-positive*' breast cancer. Women with this cancer are traditionally treated with what is called '*endocrine therapy*', which has drastically improved survival rates for the disease over the past 40 years. The story of the garden infested with weeds serves as a nice analogy for this devastating illness – the breast cancer cells are the weeds, and endocrine therapy is what the doctors use to rip them out.

Despite these efforts, around 30% of women on endocrine therapy sadly go on to relapse. Their cancer is resistant to the treatment, and can spread to other parts of the body, as the super-weeds did across the garden. When this happens, the cancer is described as '*metastatic*', and can give rise to new, secondary cancers in other organs such as the liver, brain and bones. Tragically, for these women, treatment is no longer about curing the disease, but about extending their life for as long as possible. In our research group, we try to understand what makes breast cancer cells resistant, and how we can better treat them so that one day, secondary breast cancer needn't be a terminal illness.

Resistant cells carry mutations in their DNA that make them unresponsive to endocrine therapy. Our DNA is effectively a really long sequence of about 3 billion letters, and the specific arrangement of these letters is what makes you, *you*. Sometimes, cells can make a mistake in the sequence of these latters, which we call a *mutation*. Did you notice the typo in that sentence? That's a bit like what a mutation looks like. Certain mutations in cancer cells can make them resistant to therapy, but we don't completely understand how. If we could get a better idea of what the effect of these mutations is on the cancer cell, then we might be able to find treatments that are better suited to killing them.

The super-weeds were not invincible – baking soda killed them, but it was too little, too late. Similarly, if we could identify mutations in patients as they happen, and know which therapies work well against a particular mutation, then we could give patients the best chance of a complete recovery. This concept of tailoring treatment based on the genetic mutations of each cancer is called 'targeted therapy', and it's likely to be the future standard of cancer care. In my research, I study several mutations that are found in women with secondary breast cancer and try to figure out: "What is their baking soda?".

It may still be a few years away, but I envision a future where women being treated for ER-positive breast cancer will not only have routine monitoring of their cancer's size, but also of its DNA. Ultimately, the genetics of a patient's cancer will guide the oncologist's choice of therapy. As they navigate the uncertainty of this disease, I hope that our work, and that of others in our field, will act as the trusty compass that steers them towards the path of least resistance.

SHORTLISTED

JONATHAN LEWIS

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TO INFINITY AND BEYOND: FINDING TREATMENTS FOR SPACE TRAVEL BONE LOSS

Twenty-five years from now, your typical summer holiday may have changed more than can ever be imagined. Instead of packing your sunglasses and flip-flops, getting on a plane and flying off to a sunny resort, you may be donning a space suit, stepping into a rocket and launching into orbit. Space tourism, as it is known, is a growing concept. By 2022 there are plans for the first "affordable space hotel" to be opened. For $9.5 million, up to four guests at a time (along with two trained staff) will be able to travel into orbit, spending 12 days aboard the Aurora Station, 230 miles above Earth. While this is unaffordable for you and me, there is a significant push to make space travel affordable to all, and not just for a holiday. Orion Span, the company behind the space hotel, say that their "long-term vision is to sell actual space...either for living or subleasing...to create a long-term, sustainable human habitation in LEO [low Earth orbit]." When this point is reached, we may be splitting our time between working on Earth and sleeping much higher up, in the Earth's orbit.

So, what's the problem?

The low gravity environment that is present aboard the International Space Station and in Earth's orbit will have a large detrimental effect on your bones. On average, astronauts lose 1-2% of bone mass a month in space due to less force being applied to their bones, meaning that their bones become much weaker. These fragile, porcelain-like bones will therefore buckle under much less stress, possibly shattering during day to day actions or a slight fall. Space travel bone loss (known as spaceflight osteopenia) is not the only way weak bones are formed. Large amounts of bone loss also occur following menopause, where 20% of bone can be lost within five years, or in elderly individuals. All bone loss causes the same complications, and therefore treatments are required to fix the bone.

In all forms of bone loss, your cells that produce bone (osteoblasts) slow down, being outperformed by bone-eating cells (osteoclasts). This shifts the balance of bone protection towards bone damage, where more bone is destroyed than produced, making the bone much weaker. Bones can then be broken more easily, costing the government millions of pounds a year in fixing fractures and in many cases changing patients' lives meaning they can no longer look after themselves and carry out day to day jobs. Current treatments are mainly focussed around bisphosphonates, a medication which incorporates into the bone and is taken up by osteoclasts, causing them to die and therefore stop destroying bone. However, bisphosphonates are not the perfect solution. Aboard the International Space Station, astronauts taking bisphosphonates only had a 50% decrease in the amount of bone lost.

My mission is to find new, effective treatments which can reduce bone loss, protecting not only elderly bones, but also the bones of us all during long-term space travel.

Aboard the International Space Station, some work is being carried out to aid this. In the low gravity environment, osteoblasts and osteoclasts are grown by the astronauts. How these cells change their behaviour in space are then explored, helping to discover how these changes can be targeted or reversed through therapies, ensuring bone can continuously be maintained.

What I am researching is a little more down to earth.

Using whole knee joints from patients who have gone through joint replacement surgery, I extract osteoblasts to see how well treatments alter their bone-producing activity. When osteoblasts are grown on a plastic surface, they begin to produce small amounts of bone, which I can observe and measure. I then add new treatments to the cells to see if they alter the osteoblast's activity, leading to the production of more bone. I can also look inside the osteoblasts, splitting them open to investigate their DNA. By examining the genes and proteins that make an osteoblast happy and ready to produce bone, I can explore if treatment increases their presence inside the cell and causes higher levels of osteoblast activity.

I also measure the impact of drugs on the bone-destroying osteoclasts. Since these cells eat away at bone, they need to be grown on a bone-like surface to measure their activity. Whilst artificial fake bone can be used, I get the most lifelike reactions using ivory (don't worry, I'm not a poacher!). When elephant tusks are confiscated at customs after attempts to smuggle them into the country, rather than them being burned and wasted, I use them for the good of science. The tusks are cut into small circular pieces on top of which osteoclasts can be grown. I then measure the amount of bone that has been eaten by the osteoclasts, by seeing how much is removed. New treatments can be added to the osteoclasts to see if they reduce the amount of bone eaten and are therefore effective at reducing bone destruction.

If these drugs show a positive result when added directly to the osteoblasts or osteoclasts, they need to be tested in more lifelike conditions before we can begin to explore their impact in humans. To do this, mice studies are used, where the drugs are given, and bone growth or destruction is measured by a tiny CT scanner. To begin, tests are done in normal, healthy conditions to find a drug's overall impact on bone, in addition to its side-effects. We also need to use models that mimic the bone loss seen in human conditions. Currently, the mouse spaceflight training programme has not taken off, so in our lab we use a model known as ovariectomy, where ovaries are removed to initiate bone loss (replicating what occurs in women after menopause). Drugs can then be given once bone damage has occurred, testing whether they can stop the bone loss and if they are effective as a treatment.

If drugs pass all the tests, they can then be used in human studies, taking one small step towards use in the real world. Hopefully, this work will lead to the development of new therapies to stop bone loss in all conditions, from diseases like osteoporosis, to stopping spaceflight osteopenia. If this is the case, I look forward to meeting you aboard a space hotel one day!

SHORTLISTED

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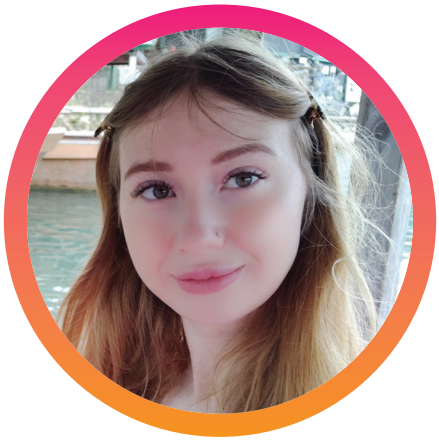

A NEW 'GOLD STANDARD' IN INFECTION DIAGNOSIS

"I think it's an infection..."

"Don't worry, I'll just take a swab now..." the doctor replies. "In the meantime..." the doctor taps on the computer keyboard and a few seconds later hands over a green prescription, "...take these antibiotics."

This is a familiar scenario to many people who have visited their GP clinic. Waiting days for your sample to return from the laboratory is often expected, yet doctors can give out medication such as antibiotics the same day. In fact, estimates suggest that as many as half of all patients who visit their GP with a cough or cold leave with a prescription for antibiotics. The majority of these infections are caused by viruses, which aren't even affected by these drugs. Reliance on antibiotics to treat infections is a key contributor to antibiotic resistance, where the drugs we use to treat bacterial infections are no longer working. Bacteria which aren't killed by antibiotics are often referred to as 'superbugs' and could result in over 10 million deaths worldwide by 2050.

Currently, the 'gold-standard' for diagnosis of infections is a process called culture, where patient samples are spread onto petri dishes in a laboratory and incubated to see if any bacteria grow. This usually takes between 48–72 hours but can even take up to 6 weeks. For many cases of suspected infections, the extended time periods required in order to identify a cause of infection could mean that the wrong treatment may be given due to the uncertainty in the nature of the infection, especially in the case of time critical infections. One of the ways to tackle this problem involves point-of-care diagnostics. Simply put, this means you'd know if you had a bacterial infection within 2 hours of seeing the doctor, but ideally whilst you're sitting in the consultation room. No more waiting for test results. No more inappropriate antibiotic prescriptions.

This is where I come in. I've been working on finding quicker ways to see if bacteria are present that are causing an infection, and identifying the type of bacteria, which can be done by using a special form of gold metal called, "colloidal gold". If you think of gold, you generally think of something shiny, expensive, and probably something that you'd wear. You'd probably think of that yellow-coloured, smooth metal. Colloidal gold is different. It generally consists of very small particles – about a million times smaller than a grain of sand – called nanoparticles.

Surprisingly, these bacteria-detecting particles aren't yellow, or even shiny. When gold nanoparticles are floating around in water, they appear as an intense red colour. When these tiny particles stick together, a purple colour is seen instead. So, how can this colour change be used in order to diagnose a bacterial infection?

First, we need to figure out how to make the gold nanoparticles stick together. Interestingly, gold nanoparticles have a positive charge, so when something is added that is negatively charged, they can stick to it, just like a magnet. As bacteria have a negative charge in their cell membrane, which is a protective layer around the bacterial cell, this can cause the gold nanoparticles to stick together – causing a visible colour change from red to purple.

In my research, I grow lots of bacteria and add it to my particles to find out the best ways of making my small device work perfectly. It sounds simple enough, but developing a diagnostic device has many issues that need to be tested before approval. A diagnostic device like mine can be based on three main concepts: it needs to be fast, it needs to be cheap, and it needs to be sensitive. Hence, in the current stages of development, the gold nanoparticle device isn't perfect. Sometimes, the gold nanoparticles stick together when there's no bacteria. Sometimes, they don't stick together even if there are bacteria. Sensitivity means I need to test this device lots of times in order to make sure that it turns purple only when bacteria is present, 100% of the time. Once sensitivity is out the way, I can then work on making this device faster and cheaper, by optimising different concentrations of particles.

Point-of-care devices like this could be useful in many different situations, such as dental practices, opticians and other community settings to diagnose a multitude of different infections. There are possibilities to apply this technology to more remote areas such as military camps or in developing countries where there are no specialist laboratories available to diagnose infections. In these rural settings, testing for bacteria is rarely done – again, leading to misuse of antibiotics and a significant contribution to the problem of antibiotic resistance. Hopefully, 10 years in the future, these devices will be easily accessible and cheap enough to buy in both developed and developing countries. Until these rapid point-of-care tests become the new 'gold standard', all we can do is ask clinicians to try to only prescribe antibiotics when needed and promote education and research on stopping the spread of these superbugs.

Let's take our same scenario back to the GP clinic, 10 years in the future.

"I think it's an infection..."

"Don't worry, I'll just take a swab now..." the doctor puts the swab into a small device on the desk. There's no colour change. "Great news, no need for antibiotics. Go home and rest."

SHORTLISTED

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THE TIP OF THE SELF-HARM ICEBERG

Almost 90% of an iceberg is hidden under water. However big an iceberg looks, it's easy to underestimate its real size. The predominantly hidden nature of icebergs is the perfect analogy for a growing global health challenge – one that is difficult to treat, and perhaps, even more difficult to understand. How do you study, let alone treat something that is mostly unseen? This global health challenge is self-harm.

I was shocked to learn that around 15% of adolescents in the UK, mainly between 12–16 years old, report self-harm. You wouldn't discover this from hospitals or clinics. In fact, most people who self-harm rarely seek professional or clinical help. Thus, many remain undetected.

As I swam through more research, I realised that self-harm is a multi-faceted issue. Broadly defined, it is the act of purposely hurting oneself with or without suicidal intent. Not all who self-harm actually intend suicide, but many suffer from increased risk of substance abuse and multiple other mental health challenges. Despite the growing awareness of the dangers of self-harm, it is difficult to predict, treat, and even talk about. Who is most likely to self-harm? How early do signs emerge? What can we do?

I began this project with my PhD supervisors wondering what the profile of a self-harmer would be. I naively thought that self-harmers would have traits researchers normally expect of those who are at high risk for mental ill health, sometimes termed 'psychopathology'. The traits that first flitted through my mind were behavioural and emotional difficulties like signs of impulsivity, depression, or anxiety.

With these expectations, we began our dive into the Millennium Cohort Study (MCS). The MCS is a large, national UK birth cohort study that provides open access to a plethora of data. MCS researchers have followed the development of almost 19,000 participants throughout the UK for more than a decade. As a researcher who is interested in child development, I felt like I had struck a potential goldmine with the MCS.

It wasn't until the participants were 14 years old that they were first asked whether they had self-harmed. Out of the nearly 12,000 participants we included in our study, close to 15% said yes. I still find that figure alarming, despite having studied self-harm for over a year. But amongst these 12,000, *who* is most likely to self-harm? To address this, we turned to machine learning techniques.

Before my PhD, I usually thought of robots when I heard "machine learning". I came to realise that machine learning actually involves algorithms that allow systems to learn from the data they are given. These algorithms can identify patterns (i.e., how variables relate to one another or how variables can be grouped together) without being told exactly what patterns to find within large datasets. That being said, it is critical to make sure the data is well organised before applying machine learning techniques – messy data in will simply result in messy patterns out.

For our study, I wanted to know whether there are particular psychological or behavioural profiles of young people who self-harm. Perhaps those who self-harm would find it hard to regulate their emotions, or perhaps they would be very impulsive.

The type of machine learning I used to find these profiles is called an 'artificial neural network'. When given data, an artificial neural network learns or 'trains' it and essentially produces a map reflecting patterns that exist across the variables within the data. In our case, our network produced a map of psychological profiles based on the behavioural, emotional, and mental health data I entered for all 12,000 participants. Participants with similar profiles (i.e., those with depressive feelings and anxiety) were placed closer together on the map but farther away from others with starkly different profiles (i.e., those without depressive feelings or anxiety).

Where do the self-harmers sit in this map? What is their profile? The answer was quite unexpected – there wasn't one uniform group of self-harmers, but two. One group fit the profile I expected, with behavioural and emotional problems and poor mental health. Strikingly, a much larger group, almost three times bigger, had no reported behavioural, emotional, or mental health issues.

We had thus come upon the hitherto submerged iceberg: the large group of adolescents who self-harm without the expected profile of 'psychopathology'. Yet, our understanding of self-harm is mainly based on the small percentage with traits like those in the smaller of our two groups: the ones more likely to seek help. The tip of the iceberg.

We dove deeper. Could we find early risk factors that lead to self-harm and, importantly, differentiate the two groups? If so, this could help shape targeted resources to intervene early on. We traced back to when participants were just five years old. The smaller group had a long history of emotional and behavioural difficulties and were disproportionately likely to be victims of bullying. The larger group, on the other hand, did not have strong risk factors until later in adolescence, at which point they indicated more risk-taking as well as unstable peer relationships. In short, not only do these two groups of self-harmers present different profiles, they also appear to have different developmental pathways.

Self-harm is a complex mental health crisis that seems to arise in the young population worldwide. The stigma surrounding self-harm alone creates obstacles to study it, let alone talk about it. There has been a surge of programmes to prevent self-harm, including anti-bullying efforts and mental health training. This is particularly important for young people who self-harm like those in our study's smaller group, with a history of psychopathology and being bullied. But as we found, there is a large proportion of young people who self-harm who may normally go undetected. It is possible that these adolescents recognise the stigma surrounding self-harm, causing them to repress or refrain from talking about the challenges they face. Probing further into why these adolescents self-harm is therefore an important future research direction.

As researchers, we have begun to dive below the surface, to discover the hidden challenges of self-harm. The unseen depths of this global mental health challenge make it a hard battle. However, alongside the dedicated efforts of clinicians, policymakers, and educators, we have hope to combat self-harm at a wider scale. With deeper research, not only can we chip away the 'tip of the iceberg' but also break the stigma of self-harm.

THE JUDGES

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