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Contents

Winner

- Saving the brain from itself 4
Scott Armstrong, Imperial College London

Runner-Up

- A step in the right direction for Parkinson's disease treatment? 6
Clare Finlay, King's College London

Highly Commended

- Molecular Fordism – manufacturing a monster 8
Ben Bleasdale, Imperial College London
- Why sugary nerves aren't so sweet 10
Oliver Freeman, The University of Manchester

Commended

- Rare genetic disease: a haystack full of needles 12
Nick Dand, King's College London

Shortlisted

- Depression in pregnancy: the elephant in the room 14
Elizabeth Braithwaite, University of Oxford
- Together they're stronger: how to combine drugs to treat cancers 16
Elizabeth Coker, Institute of Cancer Research
- Building bodies, one bump at a time 18
John Davis, King's College London
- Shaping up: what fruit flies can tell us about how our body is built 20
Clara Sidor, MRC Laboratory of Molecular Biology
- Cooking up a human 22
Helen Spiers, MRC Social, Genetic and Developmental Psychiatry Centre
- Learning to remember in Huntington's disease 24
Emma Yhnell, University of Cardiff

Winner



Saving the brain from itself

Scott Armstrong

Close your eyes and picture a high-speed car crash. An elderly relative taking a tumble down the stairs. Muhammad Ali flooring Sonny Liston, or just another late night punch-up on the streets of Soho. The common feature here is a traumatic injury to the head, resulting ultimately in damage to the brain. Such incidents are collected together under the medical definition of *Traumatic Brain Injury* – a silent epidemic responsible for close to a million visits to A&E each year, and the leading cause of death and disability in under 45's in the developed world. An epidemic which represents a major unmet clinical need, given that there are currently no drugs available to arrest the injury processes particular to this type of brain damage.

The fascinating thing about the sort of brain damage observed in a traumatic injury is that the damage caused by the initial, physical blow to the head comprises a relatively small proportion of the total damage the brain will eventually suffer. What actually happens is that in the minutes, hours, and even days following that blow, damage spreads across and into the brain, as a rot spreads through an apple. It is this damage that occurs *after* the physical insult that is responsible for the major burden of injury and the majority of deaths associated with brain trauma – reflected in the fact that a large percentage of trauma deaths occur weeks after the event.

The significant point here is that if the majority of brain damage occurs *after* the blow to the head, then there is scope for medical science to intervene: to attempt to lessen or even halt the spread of damage. Within my research group, we try to do just that; first by understanding the biological mechanisms underlying the spreading damage, and then investigating a novel drug treatment that we believe can slow it down.

The reasons underlying secondary, spreading brain damage are many and complex, but one particularly important component of the spread is a damaging biochemical cascade initiated in the brain as a result of the physical blow. In the normal scenario our brains cells communicate by throwing chemical messengers at each other across a miniscule junction; one brain cell will throw the messenger and another will receive it in a sort of catcher's mitt specific to that chemical, called a receptor.

Activation of the receptor by the messenger triggers a change in the internal biochemistry of the receiving brain cell, and the signal is carried onward. This goes on all the time and is perfectly normal. However, in the case of traumatic injury, brain cells near the site of the physical blow are torn open, allowing those messengers to flood out and go where they please.

The net result is an overloading of the receptors on neighbouring brain cells, which then become biochemically confused and begin to die from the inside out: brain cells killing themselves, essentially. Once dead, these cells will spill out their own chemical messengers in turn, kindling a damaging cascade that just keeps rolling – a rot spreading injury through the brain.

The drug we believe capable of stopping this secondary damage is a naturally occurring gas called xenon – a member of the family of noble gases, known by every GCSE chemistry student to be chemically inert. Much less well known is that once inside your body, xenon is biologically active: breathe it in and this supposedly un-reactive gas is both anaesthetic and analgesic – will both put you to sleep and prevent you from feeling pain. Xenon has these effects by blocking the activation of a particular cell receptor called the NMDA receptor, the very same receptor that is so crucially involved in the spreading damage after a traumatic injury.

We believe that by blocking the overloading of these receptors that occurs after a traumatic injury, xenon is able to prevent the biochemical confusion of brain cells and thus prevent them from proceeding along the pathway to cell death – is able to save the brain cells from killing themselves. It was in fact this serendipitous story of a chemical element practically defined by its inability to undergo chemical reactions having such a profound biological effect that first drew me to research in traumatic brain injury.

The World Health Organisation predicts that brain trauma will surpass many other diseases as the major cause of death and disability by the year 2020, largely as a result of car ownership in developing nations. Despite this, the condition remains relatively unknown in the public consciousness, and with no drugs yet available to arrest the spreading secondary injury particular to this kind of brain damage, research in the field of traumatic brain injury – saving the brain from itself – has never mattered more.

Runner-Up



A step in the right direction for Parkinson's disease treatment?

Clare Finlay

It starts small, a seemingly innocuous tremor of one little finger that you attribute to working later than usual or that extra shot of espresso in your morning cappuccino. You ignore it, assume it will resolve itself, but soon you find that you're typing extra letters on your keyboard; 'A's and 'S's and 'W's. A feeling that something isn't quite right creeps in to your mind, and only intensifies when your family notices that you've started to shuffle slightly when you walk and that your once smiley face is becoming less expressive. So you make an appointment with the doctor to see what the cause might be, and receive the news that it is probably the beginnings of Parkinson's disease.

Parkinson's disease is a neurological disorder, characterised by slowness and rigidity of movement and, perhaps more recognisably, a resting tremor. It's caused by the degeneration of a group of cells in the brain that produce a chemical called dopamine. The job of dopamine in the brain is to balance the activity of two opposing movement-related pathways; the 'direct' pathway, which acts as the accelerator and is activated by dopamine, and the 'indirect' pathway, which acts as the brake and is inhibited by dopamine.

Just as when you're driving a car, in a healthy brain this dopamine ensures that the accelerator is engaged and the brake disengaged to allow for a smooth journey. Parkinson's disease occurs when the body no longer has enough cells to produce sufficient dopamine to maintain this status, so the reverse becomes true. The brain lifts off the accelerator and leans on the brakes, slowing the person down to a crawl. Patients describe feeling as though they are walking in treacle, with slow heavy limbs that fatigue quickly. Their fingers can no longer deftly shuffle a deck of cards or open a jar of peanut butter, but instead move at an infuriatingly slow pace. Later they may find that they freeze mid-step while walking, or struggle to initiate an everyday movement such as getting out of bed.

Since the late 1960s, debilitating symptoms such as these have been treated by replacing the lost dopamine with synthetic alternatives, restoring acceleration and lifting off the brake. It sounds simple, and indeed works well for the majority of patients for several years. However as the disease progresses and more dopamine-

producing cells are lost, the connections in the brain alter, causing the circuits to misfire. This can result in sudden involuntary movements when the brain is 'on' the dopamine replacement drugs that can be as disruptive to normal life as the classical Parkinson's disease symptoms when the brain is 'off' the drugs. The next step on from this is currently invasive brain surgery, so it is clear that new drug-based treatment strategies are needed.

If we can reduce the need for dopamine replacement drugs we can hopefully delay the onset of the side effects that so often diminish quality of life within a few years of starting treatment. My research seeks an alternative way to rebalance the opposing pathways by targeting glutamate instead of dopamine. Glutamate is an essential chemical for normal brain function but when it is released in large amounts it can cause cells to become over-excited, leading them to malfunction and die. In Parkinson's disease excess glutamate is not only released in the 'indirect' pathway, thereby contributing to the excess braking in the patient's movements, but also into the precise area that degenerates to cause the disease in the first place, potentially hastening the loss of precious remaining cells. By reducing glutamate release we hope not only to manage the symptoms of Parkinson's disease but potentially to delay its progression by helping to preserve the dopamine-producing cells that are still left.

The lab that I work in has shown that by activating a family of nerve cell receptors that reduces glutamate release it is possible to protect dopamine-producing cells both in a culture dish and in the living brain. Stopping these cells from dying means that they can still produce the dopamine necessary to balance the accelerator and brake in the brain so movement is preserved. We are now trying to unravel which family member is the most important so we can target it directly.

The work I do is very early stage but hopefully it could lay the foundations for future treatments that will help maintain patients' independence and allow them to enjoy doing the things they love to do for longer. The causes of Parkinson's disease are complex, and therefore a cure may still be a distant prospect, but these small steps to treat symptoms and slow disease progression represent an important stride towards an improved quality of life for patients.

Highly Commended



Molecular Fordism – manufacturing a monster

Ben Bleasdale

Look at your phone on the desk next to you, perhaps the laptop you're reading this on, maybe a car passing outside the window or a plane overhead. All these machines were made on a production line. Each one representing a list of components, assembled in a precise order to create a series of replicas – each machine becoming greater than the sum of its parts.

Viruses are molecular machines, likewise assembled from a list of parts pieced together in a specific order. Humans weren't the first to recognise the potential of a production line to rapidly manufacture their Model T motorcars, Nature arrived at the solution first.

Embracing the ethos of mass production allows these infectious agents to rapidly clone themselves thousands of times, ultimately cannibalising their host cell in a relentless search for resources. Even for the simplest of viruses, each component must be manufactured at the right time and then precisely positioned in each infectious duplicate.

This miraculous transformation of molecular spare parts into beautifully-crafted viruses is being studied by researchers across the globe, probing for opportunities. Much as the proverbial “spanner in the works” can bring a production line grinding to a halt, a well-placed strike can likewise sabotage a virus infection. Many of our most successful anti-viral medicines work in this way, yet viruses are evolutionary acrobats and the search for the next target is perpetual.

My own research focusses on Herpes viruses, a vast family of microbes which infect virtually every animal on Earth – from humans to tortoises, oysters to whales. Once we're infected, these viruses conceal themselves deep within our nervous system where they will remain for our entire lives. Unlike hit-and-run infections such as flu, these invaders become cohabiters in our own bodies, stalking us all the way to the grave.

This family is one of the most successful viruses on the planet, estimated to have infected 60–95% of humans. Lurking within us for decades, it is known that Herpes viruses not only cause their own disease, but can also open the door to other

infections such as HIV. Across the developing world, the spread of Herpes infections has become a major influence on the HIV epidemic. An effective treatment could therefore produce a domino effect across many diseases, and the assembly process is an ideal target for this intervention.

The entire construction of these infectious agents is dictated by their most important cargo – the genetic material residing at their core. Made of DNA, like our own genome, this set of blueprints details exactly how to manufacture the next wave of viruses. Surrounding this delicate DNA is a rigid shield, called a capsid. Made of perfectly interlocking pieces, this capsid bolts together to defend the genome from damage and detection during its onward journey.

At the next step of the production line, this capsid is coated in a layer of mass produced proteins – a molecular toolbox that will help the virus establish itself in the next host. Finally, at the end of the line, this entire assembled unit is wrapped in a membrane which will provide protection from the outside world. This membrane is studded with a constellation of molecular hooks that will specifically attach the virus to its next host, and help it force its way inside.

My research seeks to understand more about the carefully orchestrated process which brings these parts together, and how we might disrupt it. In the lab we can label individual parts with glowing tags, allowing us to observe new components being manufactured and sequentially assembled into developing viruses. High-powered electron microscopes let us peer deep inside infected cells, following the interactions on the assembly line at a molecular level – helping us piece together the story of viral mass production.

In addition to discovering more about the virus, we are simultaneously learning more about ourselves. Viruses manipulate, subvert and co-opt our cells into becoming factories for their own replication. This interaction can reveal secrets about our own biology too, both during health and disease. Armed with such knowledge, we are better prepared to tackle diseases caused by our own malfunctions, rather than just by infections. In this way viruses are great educators, teaching us as much about ourselves as we learn about them.

By studying the production lines for these molecular machines, we can begin to reveal their weaknesses. Millions of years of evolution have honed these viruses into Fordian masterminds, capitalising on the benefits of mass production to a level that humans are only beginning to imitate. The task of understanding such complexity is daunting, but it holds significant potential for improving global health. So there's good reason for us to be industrious – each step forward is adding one more proverbial spanner to our toolbox.



Why sugary nerves aren't so sweet

Oliver Freeman

Strewn across my desk are big sheets of A3 paper. Like sprawling cobwebs, lines criss-cross all over them, splattered with a traffic light system. These are diagrams showing the pathways of metabolism. Built up over decades, they describe what happens to chemicals in your cells, and how cells make energy from them.

The traffic light system is for me. It tells me which chemicals go down (red), which do not change (yellow) and which go up (green). I am interested in diabetes, and more specifically the impact that it has on energy generation in the nervous system. The colours denote the differences between diabetic nerves and healthy nerves.

Sugary nerves may sound like a marketable new pick-n-mix sweet but if this happens in the body, it can cause disastrous consequences. We all know that diabetes results in high blood sugar. What is less well publicised however, are the effects that diabetes has on the rest of the body.

When sugar levels rise in diabetes it is because sugars cannot get into your muscles and so end up circulating the body instead. To enter your muscles sugars need insulin, which is not present in type 1 diabetes and doesn't work properly in type 2. This means that there are vast amounts of sugar swirling around the body. This sugar soaks into specific organs and tissues of the body and causes damage. The most common part of the body impacted this way is the nervous system and nerve damage such as this is known as diabetic neuropathy.

Diabetic neuropathy is a nasty condition as it can cause sufferers to feel agonising pain in their hands and feet, or it can cause them to feel nothing at all. Perhaps you're thinking the latter is preferable, but when you can't feel anything in your feet, there's a high chance of being oblivious to a cut. This cut may get infected and before you realise it, the foot is too infected to stay and needs to be amputated.

Normally, sugars are used as the primary source for energy generation in your cells. All my charts of metabolism spiral around sugars. Hypotheses about how excess sugar causes nerve damage are plentiful but experimental treatments targeted at these have yielded disappointing results in clinical trials. For this reason, what my work aims to do is to generate new hypotheses by going back to square one.

We have performed an untargeted, 'shotgun' approach to measure as many of the chemicals in the nerves as we can. What we measure is not biased by how people think neuropathy might develop, and so it allows us to start a clean slate. By measuring the chemicals in healthy nerves and diabetic nerves in a mass spectrometer, we can build up a picture of what is happening within them, and how they are generating their energy. My way of doing this is reading off the values for each chemical, finding it on the chart of metabolism, and highlighting it in a traffic light system.

To fire electrical signals up and down them all day, nerves need to generate a lot of energy. What my traffic lighted cobwebs tell me is happening is unsurprisingly, sugars increase a great deal in diabetic nerves. What is interesting is that despite this increase in sugars, there isn't an increase in energy generation. Instead, a lot of this sugar is being converted to fat. Following the lines that lead from sugars to fats, you can see a lot of the chemicals in green.

What becomes of these fats is worrying. The typical way people think about metabolism is in terms of weight gain and loss. If you eat more calories than you need, the excess will be converted to fats which will be stored around the body. If you eat less calories than you need, these fats will then be broken down to generate energy.

Unfortunately, this doesn't appear to be the case in the diabetic nerve. To the other side of these green highlighted fats is lots of red, showing the breakdown of fats to create energy is failing. What appears to be the case is that not only are the sugars not generating the energy needed, neither are the accumulating fats.

So why does any of this matter? Well, what this research has done is to create a number of new hypotheses to test. It has given us and others some new ideas as to why diabetic nerves might be failing. It has given us new ideas for treatments and it has given us new ways to test other new treatments. I hope that by correcting some of these reds and greens, perhaps we can make a real push towards better management of nerve damage.

Commended



Rare genetic disease: a haystack full of needles

Nick Dand

Finding a needle in a haystack is – presumably – not easy. But in theory, with enough time and a lot of patience most of us could probably manage it, especially if we cheated a bit (with a magnet?). So let's make the problem harder. Now we've lost our needle in a haystack which already happens to contain hundreds or thousands of other needles, all subtly different in shape or size. Even if we can pull out all of the needles we're stuck: how can we find our needle when they all look so similar?

Identifying the genetic mutations that cause rare diseases feels a lot like the “too many needles” problem.

Recent technological breakthroughs mean we can now read a person's entire genetic code, the blueprint found in every cell that guides how our bodies develop and function. It is a sequence of three billion nucleotides (which can be A, C, T or G) and is organised into units called genes, each having a specific function. Most of the code is identical from person to person (that's what makes us all humans) but a tiny fraction can vary (that's what makes us *different* humans).

A tiny fraction of three billion is not insignificant: we each carry upwards of a million sequence variants – for example a 'C' nucleotide where most people have a 'T'. For genetic diseases, just one sequence variant can make all the difference. While most genetic variation is harmless, a variant in a critical position can cause a bodily function to fail and lead to disease. Cystic fibrosis is an example of a relatively common disease that is caused by mutations in a gene named CFTR, and our understanding of this causal relationship is of great benefit when it comes to diagnosis and treatment.

For many less common genetic diseases, however, we are yet to identify the sequence variants responsible – despite their often devastating consequences, like developmental problems that leave newborns little chance of survival. Reading a patient's genetic sequence is a start, but the problem now is that we have *too much* data; since there are so many sequence variants we can't easily tell which one causes the disease. Genetic sequencing technology has done a wonderful job of dispensing with the haystack altogether, but has left us knee-deep in needles.

This is the challenge that I face in my research. I am not a biologist in the conventional sense, but a mathematician-turned-computer scientist working in genetics. The volume of data now generated in this field is vast, and making sense of it all is one of the biggest challenges in the immediate future of genetics research. My goal is to build computational tools to analyse genetic data, picking out the noteworthy sequence variants from the rest. Tools that do this well are in great demand by the biologists and medics that study individual diseases.

With this “too many sequence variants” problem I can benefit from the progress made by others. For a number of rare diseases, a simple but powerful approach has identified the sequence variants responsible: read the genetic sequences of a handful of patients and find the only rare variants shared by them all. In haystack terms, this might equate to searching a number of haystacks for a matching set of needles.

Sadly, though, this doesn't always work. There may be no single gene implicated in all of the patients, and it is this scenario that intrigues me. After all, genes do not carry out their tasks alone; they interact, working together to keep our various bodily processes running smoothly. So could a disease caused by some malfunctioning process not result from a sequence variant in any of the genes involved? With this in mind, I work on tools that take the patients' sequence variants and add yet more data, this time from databases containing thousands of known gene interactions. What they look for are groups of genes that work together but carry a sequence variant in all of our patients. Our matching set of needles no longer have to be identical, just all of the same “type”.

It's a difficult task but if we can find these groups they will tell us much about the roles of the individual genes involved and the function they perform together, crucial information if we are to develop better diagnosis and treatment options for these rare diseases. The benefits could reach further than this, however. Understanding how genes work together in simple cases is a great first step towards understanding the genetics of common diseases like diabetes or heart disease, which result not from a single mutation but from sequence variants in tens or hundreds of genes, or even more.

Just don't ask me to explain that in terms of needles.

Shortlisted



Depression in pregnancy: the elephant in the room

Elizabeth Braithwaite

Two blue lines. The result I have been waiting for, hoping for. So why am I not pleased? In fact, why am I so unhappy? Perhaps it's the realization that my life will never be the same again. No more late night partying or spontaneous weekends away with friends. Or perhaps it's just the dramatic change in hormones that come hand-in-hand with pregnancy. Either way, I can feel the floor is slipping away beneath me as I begin to spiral downwards into a dark void of misery. I can't eat, can't sleep, or even manage a smile. The worst part of all is I can't tell anyone I'm depressed... because I'm supposed to be glowing.

Postnatal depression is routinely screened for and widely accepted as a serious risk to both the mother and the baby's development. Most people don't realize however is that depression *during* pregnancy is actually more common. It could be caused by a serious life event such as the death of a close relative, a continuation of depressive symptoms from before pregnancy, or could occur for no apparent reason at all. It is estimated that around 30% of women experience a bout of depression whilst pregnant. That's huge. So why don't we know more about it? A likely explanation is because of the social pressures placed on pregnant women: they are *expected* to be glowing; this is *supposed* to be the happiest time of their life.

So why should we care more about mental health in pregnancy, it doesn't affect the baby right? Wrong. Recent research has shown that depressed pregnant women are at increased risk of having a premature and low birth weight baby, which is linked to diabetes, obesity and heart disease in adulthood. Further, the infant is also more likely to have behavioural and emotional problems in childhood, and a psychiatric diagnosis in adulthood. This was evident when postnatal depression and genetics were accounted for, which indicates that something is going on biologically within the womb when a mum is depressed, which causes these adverse infant outcomes.

So how exactly does low mood during pregnancy affect the baby's development? Well, that's the million-dollar question in this field, and we currently don't have a good enough answer. A popular theory at the moment is that depression alters the

mum's stress-response system, which is called the Hypothalamic-Pituitary-Adrenal (HPA) axis. The HPA axis is activated when a person is stressed, and results in the release of cortisol, the main stress hormone, into the blood. The current theory is that this system is over-active in depressed pregnant women, so more cortisol is released into the blood than normal. This excess cortisol then crosses the placenta, enters the fetal blood circulation and alters the development of the baby's HPA axis so that it is permanently over-active. There is already some evidence to support this theory: infants born to mothers who were depressed whilst pregnant have over-active stress responses. Also, infants with some behavioural and emotional problems, and adults with psychiatric disorders have over-active stress responses. What we don't know for certain is how, or even if, the HPA axis of depressed pregnant women is altered.

This is where my research comes in: I am attempting to fill the gap in this theory by investigating how the HPA axis of depressed pregnant women may be different from non-depressed pregnant women. I am currently recruiting depressed and non-depressed mums-to-be to take part in a study which is examining the diurnal (daily) pattern of cortisol release, and also how the HPA axis responds to mild stress. To do this, my participants watch a short video showing clips of babies crying, which induces a small amount of stress. Before and after watching this video, participants produce saliva samples, from which I measure the levels of cortisol, and see how the HPA axis may be different in the depressed and non-depressed women. Then, 2 months their babies are born, I also collect saliva samples from the infants before and after their first injections. This also allows me to see whether depressed mothers with over-active stress responses during pregnancy, also give birth to infants with over-active stress responses.

Understanding how depression changes pregnancy physiology is extremely important. Depression during pregnancy somehow affects the developing baby, so understanding the underlying physiology is the first step towards identifying an effective intervention. It is estimated that 20% of the behavioral and emotional difficulties experienced by children, and a significant number of psychiatric disorders in adults, can be attributed to their mother's depression whilst pregnant. So, if we can develop a new prenatal intervention for depression (because there are also worries about prescribing antidepressants in pregnancy), we could potentially prevent the onset of these disorders in thousands of individuals, before they are even born.



Together they're stronger: how to combine drugs to treat cancer

Elizabeth Coker

Some things are just better together: fish and chips, strawberries and cream, apple crumble and custard. Cancer drugs are the same. There are often many good reasons for using combinations of drugs: they can produce a better response than using just a single drug, and, crucially, they can prevent a tumour developing drug resistance. When fighting against this destructive disease, no one wants to lose a weapon from their armoury.

As with combinations of flavours, scientists often don't really understand why certain combinations of drugs work so much better than the sum of their parts – they just *do*. Some of these combinations produce good results in the patient as the drugs target different parts of the same process, which gets hit with a double whammy. Other combinations may work well due to a property known as synergy: for example, if Drug A kills 20% of cells and Drug B kills 30%, together they might be able to kill 75% of cells, rather than the 50% you might expect by simply adding their effects together. This seems rather counterintuitive, but it can happen, and often we don't know why. What is indisputable is that the right combinations of drugs can be extremely powerful and produce major improvements in the prognosis of patients with cancer.

But how can we work out the best combinations to try? There are hundreds of cancer drugs in existence, so when you consider all of the possible combinations of 2 or more of these, plus combinations of all these with the thousands of other licenced medicines, there are millions of possible combinations to consider.

We could test all of these combinations in the lab one-by-one, but this would be incredibly inefficient and require vast amounts of resources. We would probably find that most combinations the students tried really don't work (like a pairing of fish and custard), with a small number that are sort of ok, but not quite the magic combination we're looking for (like apple crumble and strawberries). If we want to find the best combinations quickly and efficiently, we need strategies to prioritise combinations for testing in the lab. This is where my research comes in.

The aim of my MRC-funded PhD is to use powerful computers to predict these good combinations. I am focusing on combinations with a specific drug called

AUY922, which blocks HSP90, a protein that is crucial for the survival of many cancers. Proteins are large molecules present within cells that are involved in a huge range of processes, including signalling within the cell. Researchers at my institute developed AUY922, and it's already had great success in clinical trials. In short, AUY922 can now be part of a magic combination of cancer drugs; I just have to work out what to pair it with.

To do this I will collect thousands of measurements of the levels of different proteins within cancer cells and how these change when the cells are treated with AUY922. I will then use computational techniques to learn the probabilities of each protein in the system increasing or decreasing in abundance during and after drug treatment. This huge set of intertwined probabilities will form the core of my virtual model.

Hopefully I will have captured enough information about the proteins that my model will behave like a real cell in a real experiment. I will run simulations where each individual protein is blocked from the system in turn, followed by further simulations of all possible combinations of two of these targets. Depending on how the model responds, I will be able to predict whether targeting this protein or pair of proteins in combination with HSP90 in a tumour cell is likely to kill it faster than when just HSP90 is targeted. I can then check this in the lab: if my prediction is correct, I will pass on this suggested combination of targets to other researchers at my institute, who will investigate this new target more thoroughly. If my prediction is incorrect, I can use this information to see where my model has gone wrong and work to improve it. It will be much, much faster and more efficient for me to run these *in silico* simulations than to test all possible combinations of drugs in the lab, even if my model is sometimes wrong.

What's the significance of my work? In short, I am devising a completely new and unique tool that will enable the next magic combinations of cancer drugs to be discovered quickly and efficiently. This means that with the support of the MRC, these valuable therapeutic strategies can reach patients in need sooner.



Building bodies, one bump at a time

John Davis

There are phases in life in which monumental changes occur with sudden regularity, and I am currently in one of those phases. Recently, the frequency of friends sharing the great news “I’m having a baby!” has increased drastically. I have found myself talking a lot about nurseries with Mums-to-be, as Dads-to-be show me gleefully the gadgets and interchangeable parts on their pram. As I play with the new arrivals in my arms, and watch Dad struggle with the pram, I start to wonder.

How can a single cell create a whole being? How are our arms able to grow to the same size? How can this small baby develop into a full adult? But there is the opposite side, the dread of all expecting parents. What if it goes wrong? In order to understand how life renews and protects itself, as well as why mistakes happen, you need to understand the basic components of life. You *need* to understand cells.

Cells are the LEGO building blocks of life. They are individual units with different shapes and sizes but come together to form complicated structures, like us. Cells do this in a ‘social’ way, communicating and organising themselves through close relationships. Developmental cell biologists, like me, want to know how cells are able to collectively create complex structures like our bodies. To this goal scientists have focused on examining how cells ‘socially’ interact. The way I examine these interactions is to watch cells collide.

Just as physicists can discover fundamentals of the universe, like the Higgs Boson, by watching particles collide, analysing cells colliding helps us understand how cells recognise, talk and understand each other. All of which are essential for us to develop into an adult. The tools to look at cells colliding are different from those of particles, where we fire them at each other. To understand how cells interact with each other during collisions, we need to observe them colliding within their natural environment, the body. Luckily certain cells, such as those of the immune system, regularly collide within our bodies, in a process called Contact Inhibition of Locomotion. Wordy, I know, but this process is important in living organisms like the one I work on, the fruit-fly.

Fruit-flies have been used by scientists for over a hundred years to study how life works. In that time tools have been developed that allow us to look at and manipulate individual cell types within the fly. For my research I look at a group

of immune cells called macrophages, which are important for clearing away infections and cleaning up wounds. I have created tools which fluorescently label these macrophages, allowing me to watch them moving and colliding inside a living fly.

Since the discovery that cells react to each other whilst colliding over 50 years ago, it has been unclear why this is important for development. Recently, I have shown that patterns emerge when cells collide, allowing tissues to take form. Colleagues have also shown that this process can help neurons navigate allowing them to form our neural circuitry. It can even help cells move to the correct location for them to do their job, such as cells which develop our facial features.

The techniques I have developed to look at cells colliding allow me to probe the steps choreographing this process. This will allow us to learn the 'social' rules for forming patterns and complex tissues, such as the brain. I have started to realise that the physical properties of cells, such as their hardness, plays an important role in determining how they work together during collisions. Do these physical properties affect how cells communicate? Do they help them organise themselves? Answering these types of questions are essential to understanding how cells behave to create organs, repair damage or spread out, guarding against infection. Furthermore, research into other aspects of development has already shown that the shape of cells can affect whether cells form bone or fat, highlighting the need to understand the physical world of cells.

By answering questions of development, through looking at cells colliding, new discoveries are being made which alter how we think cells organise themselves. This allows us to slowly start to understand how cells can form tissues or how they heal and protect us from invaders. In the short-term, this understanding could help develop techniques for stopping diseases caused by cells misbehaving, like cancer or auto-immunity. Ultimately, it could help us develop new medical techniques such as tissue regeneration, stopping the complications and shortages of organ donations. These applications could be a long way off and can seem like science fiction, but all of the research needed to make this a possibility begins with understanding the cell, and that's why my research matters.



Shaping up: what fruit flies can tell us about how our body is built

Clara Sidor

Stretch your arms up... take in a deep breath. It is Sunday, and you are headed for a jog along the river. The fresh air enters your lungs, you are full of fuel from the eggs on toast your intestines have digested this morning, and you start: left, right, left, right, breathing in rhythm as your muscles propel you forward and your heart rate increases.

It is striking, and almost unbelievable, to think that the highly complex and organised machine that is your body started off as a shapeless microscopic ball of cells looking like a bunch of jelly drops, the embryo. As building blocks of the body, those cells multiplied and organised themselves into a variety of organs of different shapes: from the flat sheets of your skin, to rounded organs like your liver or heart, or tubes such as your intestines, blood vessels, and the microscopic tubes in your lungs and kidneys. How do cells build all these different forms? What forces shape the embryo? These questions have puzzled biologists for over a century and have given rise to the research field of morphogenesis, from the Greek “*morpho*”, which means shape, and “*genesis*”, which means the origin.

In order to tackle these questions, scientists have turned their attention to model animals such as the humble fruit fly. Fruit flies are easy to breed in a laboratory, and just like us are made of cells, which contain very similar molecules to the ones found in our cells. Because flies lay eggs, their embryos are easily accessible for study. Recent advances in microscopy techniques have made it possible to film in great detail the development of live fly embryos, which has revealed the fascinating choreography of their cells: moving, pushing, pulling, sculpting the embryo.

I am trying to understand how cells build tubular organs by studying the formation of the fly embryo salivary gland. Movies of this process reveal how, in less than two hours, a flat sheet of cells on the outside layer of the embryo contracts and forms a dimple, which is then pushed into the embryo to form a tube. Through experimentation, scientists in my laboratory and other laboratories have started to unravel the underlying mechanisms of these cell movements.

Far from being jelly drops, cells are highly organised. Each cell contains a skeleton of multiple protein fibres that maintains its structure. One important type of fibres is made from a protein called Actin. Another important molecule is a protein called

Myosin, which is from the same family as molecules that cause muscle contraction. Myosin is able to bind to, and pull on the Actin fibres, creating a force that can maintain or change the cell shape.

Moreover, Actin and Myosin are able to form bundles of fibres that are connected across many cells, creating a pulling cable that can change the shape of a large group of cells. My laboratory has discovered that cells forming the salivary gland of the fly embryo assemble a cable of Actin and Myosin around themselves. This cable pulls the cells together like a lasso rope, and pushes them into the embryo to form the gland tube.

By filming live fly embryos under a high-resolution microscope, I am investigating how salivary gland cells are able to build the cable at just the right place and the right time, and if other cells within the embryo use similar systems to form other organs.

This type of research belongs to the category of basic biological research: an exploratory branch of research that is aimed at understanding biological phenomena. In contrast, applied research aims to utilise the knowledge acquired through basic research to find applications such as understanding a disease and finding a cure for it. Basic research is therefore crucial as it provides the advances in knowledge that applied research builds on. For example, most of the biological molecules that cause cancer to develop were first discovered in the fruit fly by biologists interested in understanding how animals grow. The molecules I am studying in the fly are present in all animals, including humans. My research will therefore allow a better understanding of how organs form, not only in fruit flies, but also in ourselves.

In the future, understanding how organs are built could have great implications in the emerging field of regenerative medicine. Scientists are already trying to use cells to construct new organs for patients whose own organs have been damaged by disease or trauma. Perhaps more importantly, the study of fruit flies may help us answer the fascinating questions of how our bodies are built, and what made us what we are.



Cooking up a human

Helen Spiers

As you read these words, the 50 trillion or so cells of your body are busy working together, allowing you to breathe, digest your last meal, think, reach for that cup of tea...You are the product of cellular teamwork on a huge scale. Things weren't always this way though. You were once a single cell bequeathed with a unique genome inherited from your parents – your DNA. That one cell divided into two, these cells divided again and again, to eventually form you, replicating your genome with each division so that every daughter cell could have their own copy of your unique set of genetic instructions.

So if each of your cells inherited an identical copy of your genome, why didn't you become a homogenous blob as those cells divided? Take a look in the mirror; you are formed of trillions of molecularly unique cells performing very different biological functions. How are these cells able to do such different things while working from the same basic blueprint? How cells divide and differentiate into complex multicellular organisms is the subject of my research—I study the epigenome.

The epigenome is an additional layer of information that sits on top of your DNA. Its biological function is to tell your cells which genes they should express – the epigenome helps your cells interpret the instructions contained in your genome. This is a complicated concept, so I'll try to make things clearer with an analogy. I like to think of the 46 chromosomes of the human genome as a set of cookery books that contain the recipes to make you. You received half of these, 23, from your Mum, and 23 subtly different ones from your Dad. Unless you have an identical twin, this particular set of recipes is unique to you, and it is highly unlikely it has ever existed before. Each cell in your body has a complete set of these cookery books and the recipes they contain are used by your cells to make proteins.

There are roughly 30,000 protein recipes in total. Unsurprisingly, not all of these recipes are needed by all of your cells all of the time. The different cells of your body; your skin, brain, liver cells etc. are like restaurants that all have a copy of the same cookery book, but use different combinations and amounts of the recipes contained. It is this that makes the cells different, and able to serve distinct biological roles within your body despite possessing identical genomes. So how do our cells know which recipes to use? This is where the epigenome is introduced into

our analogy; your epigenome is added on top of your genome, like sticky notes onto the pages of a cookery book, to indicate whether a particular recipe is needed or not.

This analogy helps to explain some of the key features of the epigenome. Like sticky notes added to pages, epigenetic additions to your genome don't alter the underlying instructions. This is really important as the recipe may be needed again in the future; which brings me to the second key feature of the epigenome – it is reversible. Using our analogy again, the sticky notes can be removed – allowing recipes use to be increased or decreased according to need. Finally, the epigenome can be copied along with the genome when a cell divides – the sticky notes can be transcribed alongside the cookery book. This allows daughter cells to maintain production of the same recipes as their mother cell – so muscle cells remain as muscle cells, liver cells remain as liver cells etc. which is essential for the development and maintenance of different tissue types.

Your epigenome plays a crucial role in regulating how the instructions contained in your genome are used. You, in all your complex multicellular glory, wouldn't have been able to develop from that original single cell without it. And if that weren't enough to convince you why studying the epigenome is interesting and important, epigenetic dysregulation – when epigenetic mechanism go wrong – contributes to the development of many diseases, from diabetes and cancer, to autism and Alzheimer's. Through studying how the epigenome is altered in disease we can improve our understanding of what has gone wrong, and begin to develop ways to put things right. Because the epigenome is reversible, therapies targeting it have the potential to reverse the biological changes seen in disease. The discipline of epigenetics is a huge one – every single cell in your body could potentially have a unique epigenome that varies as you develop and age. Research so far has barely scratched the surface, however it is already apparent that epigenetics holds great promise for understanding how the recipes of life were used to rustle you up.



Learning to remember in Huntington's disease

Emma Yhnell

Imagine you have just received the results of a genetic test, it has confirmed the devastating news that you have been dreading: you will develop Huntington's disease. You now have to live with the life changing knowledge that over the next twenty years the parts of your brain that control your personality, memory and movement will slowly melt away. You will no longer be able to look after yourself and you will eventually die.

1 in 10,000 people in the UK have Huntington's disease. The cruel nature of this disease means that there is a fifty percent chance that you have already passed the disease onto your children, the very people who may care for you while the disease takes hold in your final years.

Try squeezing your hand into a tight fist, release it then clench it, do this again, now faster and faster. After a while the muscles in your hand will begin to get tired and ache. Imagine this same ache but now in every muscle of your body, from the muscles in your shoulders all the way down to the muscles in your feet. This is how somebody in the late stages of Huntington's disease feels. They have lost control of their motor co-ordination and are unable to complete everyday tasks like brushing their teeth, getting dressed and talking to family and friends.

Scientists know that a defective version of a gene called *huntingtin* causes Huntington's disease. We need the *huntingtin* gene to develop and survive, but people with Huntington's disease have a faulty version of this gene which is too long – it has become expanded. The expanded gene makes a protein which is similar to the chain of a necklace, it becomes tangled and knotted and is incredibly difficult to undo. These knotted clumps of protein, called aggregates, build up in the brain and interrupt the chemical messages that control the body and mind.

So, if we know the genetic cause of Huntington's disease, why is there still no cure? The main reason is because we still do not fully understand how this faulty gene affects the brain. Therefore, if we can increase our understanding of how the defective gene affects the brain and why it causes the symptoms that we see in patients we can seek to effectively treat the disease.

To do this, my PhD research aims to investigate the behaviour of mice with Huntington's disease to see if they accurately replicate the human disease. I specifically focus on the subtle early changes in behaviour that occur during the development of the disease. This will allow us to target Huntington's disease with potential treatments as early as possible to prevent the debilitating physical symptoms that occur in the later disease stages.

Patients with Huntington's disease have problems with their working memory early in the disease progression. Why is working memory important? You use it in your everyday life, for the temporary storage of information. Mental arithmetic is a good example, if I asked you to add £1.75 and £2.30 without writing it down you could probably tell me the answer relatively quickly. But if we break this task down, we can see how it requires working memory. First, you have to listen to the numbers and remember them. Next, you add them together to find the answer. Then, you remember the answer and tell me that you have done it. The correct answer is £4.05! A task which you may have thought seemed quite simple actually requires several regions of your brain to work together. In a patient with Huntington's disease these particular brain regions are no longer able to communicate and work collectively and this is why patients have problems with tasks of working memory.

I have designed a task to test working memory. The aim of the task is to learn to touch an illuminated light, remember the initially touched light and then, after a delay, learn to touch the same light again when presented with other additional lights. We can use this task to see if mice with Huntington's disease develop problems with their working memory during disease progression. We can then test potential new therapeutic treatments to see if they can restore working memory and improve task performance.

As a researcher I can get caught up in the complexity of my work. I might get frustrated when my experiments go wrong and I can all too easily forget why my research is important, but then I stop and remember why I do what I do. I want to help real people who are currently suffering from this disease and future generations of people who will develop it.

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