



Max Perutz Essay Prize 2010: WINNER

Wanted: Dead or Alive

Nicola Harris

My palms are sweaty and my mouth is dry, but it's more excitement than nerves, though of course the nerves are there too. I've got my cells out of the incubator and now I just can't resist having a quick glance at them down the microscope – will I see more dead cells floating in one set than the other? I know I can't tell properly till I add some staining solution and analyse them accurately, but that will take hours and I just can't wait that long to find out: has it worked or not?

If you've ever held that envelope of exam results and been desperate to tear them open and find out how you did, but also terrified to look in case you didn't get what you were hoping for, then you'll know exactly the sort of feelings I'm talking about.

I'm working on tumour cells from 2 childhood cancers, called neuroblastoma and Ewing's sarcoma. These are both very hard to treat, with less than half the children surviving for 5 years after their diagnosis. That's the problem with treating cancer, some patients do brilliantly on a particular drug, but for others it'll have little effect. At the moment it's often a case of trial and error working out which drug is going work – and some people simply run out of time before we can find the right one. So what I'm trying to find out is what causes the differences in responses and how can we use that to our advantage.

The drug I'm using is called fenretinide, and it's similar to vitamin A (the vitamin found in carrots). It's able to kill cancer cells, whilst normal cells remain healthy. It works by causing a build up of oxidants in the cells (you'll all probably have seen the adverts for beauty creams offering anti-oxidant properties to get glowing skin – that's because oxidants are bad news for cells!) Normal, healthy cells should be able to cope with the presence of a few oxidants, but cancer cells will already be exposed to high levels as they're produced when cells divide, and so they can't cope with the extra oxidants produced from fenretinide treatment.

Due to its similarity to vitamin A, fenretinide can get into receptors meant for that vitamin and so the main side effect with fenretinide treatment is that the patients get what's called night-blindness; basically, you can't see very well in the dark. This makes it particularly suitable for treating childhood cancers as it's a much easier side effect to deal with than many other treatments – it's easier to give a 5 year old a night light than to comfort them as they're losing their hair. The problem is that fenretinide seems to work really well for some neuroblastoma and Ewing's sarcoma tumours, but not others. And I want to know why!

I've found that some of the tumours have more of an enzyme called CYP26 than others, and this enzyme helps to metabolise fenretinide in the body. Usually, you'd expect the patients to do worse if their body is breaking down the drug, but fenretinide is a little different. As well as the drug itself being able to kill cancer cells (what we call an 'active' compound), one of the metabolites of fenretinide is also active. This means there could be an extra hit from this second compound to those cancer cells where there is metabolism occurring. This is the reason I'm desperately hoping to see more dead cells in some of my flasks than others – these should hopefully be the cells with more CYP26.

So what would it mean if I'm right about the link between CYP26 and how many cancer cells die? There are a few options actually – we could be selective and only give the drug to those whose cancer has been tested and shown to have CYP26, or there are other drugs which have been shown to increase concentrations of CYP26 in the body, so alternatively these could be used in combination with fenretinide. The important point is that we could decide on which drug or combination of drugs to use based on what should work for each particular patient, and that's what this is all about – taking the guess work out of cancer treatment.

I've already analysed these cells to see how much CYP26 they have, and then I've added the drug to them and left them to grow for a few days (having a quick peek everyday to see how they're getting on!) Now it's the moment of truth, as I look down the microscope and bring the cells into focus.....



Max Perutz Essay Prize 2010: RUNNER-UP

Spinal Muscular Atrophy: worming our way towards a cure

James Nicholas Sleight

Imprisoned. Trapped. You are in a full-body straitjacket. You can just about wiggle your toes. Your neck muscles have become so weak that raising your head has become like trying to heave a boulder up an ice-covered mountain. You can hardly even swallow and keep descending into fits of uncontrollable coughing. Breathing, laboured, an all-consuming, monumental task.

This is what it is like to be a baby with severe Spinal Muscular Atrophy (SMA), a devastating disease of the nervous system. SMA strikes 1 person in 6,000 in the UK, which makes it about ten times more common than getting five numbers on the lottery. Type I SMA, the most formidable and widespread manifestation of the disease, is the principal genetic cause of death in children less than two years of age. Of the babies that draw this unlucky number, about 80% will not even see their first birthday and only 5% live to 18 months of age. The disease is brutally debilitating, progresses much faster than most cancers, and there is no cure. Basic physiotherapy can only marginally reduce the suffering of those young children sentenced to a cruelly premature death unlikely to ever utter their first words.

SMA results from an incomplete genetic instruction manual. Specific information is lost on how to build healthy motor neurons, which are the nerve cells that send electrical signals to muscles from the spinal cord allowing conscious movement. An inherited fault in DNA prevents the production of a fully functional protein called Survival Motor Neuron (SMN). SMN is found in every single cell of the body, not just the nerves, and at all stages of life. As its name suggests, when the SMN protein is reduced or dysfunctional, it causes the specific deterioration and death of the motor neurons. This means that these nerve cells are no longer able to excite their target muscles, so the muscles shrink and wither (atrophy) like a plant without water. Despite your brain containing around 100 billion neurons, the mind is unaffected by the disease, so babies with Type I SMA are still able to smile and convey emotion by facial expression.

The SMN protein is so vital to life that every organism studied to date has been shown to possess its own copy. Cats, mice, fish, and even simple, single-celled

yeast have SMN. This makes it easy to study SMA and the function of the SMN protein using cellular and animal models that mimic particular aspects of the disease.

In my research I make use of a self-fertilising, or hermaphroditic, worm called *Caenorhabditis elegans* that feeds on bacteria and usually lives in the soil. Smaller than a grain of salt and with the ability to very quickly produce large numbers of offspring, *C. elegans* is easily grown in the laboratory at relatively low cost. Very surprising to most, this humble worm, even though it is distantly related to humans, shares approximately 70-80% of its genes with us. These characteristics of *C. elegans* make it an ideal organism with which to perform rapid, large-scale experiments using many worms. I have recently characterised a new *C. elegans* model for a mild form of SMA by measuring many different behaviours that are affected by a mutation in the worm SMN gene. This new model has a reduced lifespan, impaired neuromuscular function, and is less mobile, all aspects resembling symptoms of the disease seen in SMA patients.

The complete lack of an effective treatment for SMA is the driving force behind my research. Using the *C. elegans* model, I am sifting through a carefully chosen library of drugs, looking for substances that improve the worm's movement defect in the hope that I may ultimately find an effective treatment for patients with SMA. The vast majority of the drugs in the collection are already approved for safe use in humans, which could speed up the time it takes for one of the very best to get from the laboratory to the clinic. Through numerous rounds of screening to highlight the most promising candidate drugs, I have found six that appear to specifically recover mobility of the SMA model. I am currently testing the capacity of these six drugs to ameliorate other defects of the worm in order to identify the most promising compound for further study.

I do not expect to find a miracle cure for a disease with such complex and unknown underlying mechanisms. But, if I can identify a single drug with some benefit, it could perhaps begin to prise open those bars, loosen those shackles and improve the quality of life of those bright-minded SMA babies trapped inside disabled bodies.



Max Perutz Essay Prize 2010: **COMMENDED**

Surgery-sparing science: Moving away from the cutting edge

Neil Rajan

We both wanted the same thing, to save her scalp. I was sitting opposite a young woman with numerous tumours on her scalp. Around the table sat female relatives, who had already undergone complete scalp removal, and now wore wigs. The atmosphere in the clinic was mixed with anticipation and guarded optimism. Unsaid but apparent - what will this new doctor offer? Will it be more surgery? Only a few years ago, the rare, abnormal gene which ran in this family resulting in hundreds of tumours on the scalp, was discovered. Recently a further breakthrough had been made, and the possibility of treatment with drugs like aspirin was raised. As a trainee dermatologist, I had been invited to this genetics clinic to meet the affected patients and explore this possibility.

I quickly learned from meeting several families who carry this abnormal gene, that this condition was cruel. Both men and women have an equal chance of inheriting the abnormal gene, yet it is the women who appear to be more severely affected, requiring scalp surgery more frequently. Tumours appear after puberty, and are thought to originate from hairs that acquire an abnormal growth signal, which results in a tumour being formed instead of a hair. Initially a few grape-sized lumps appear and soon they enlarge and can no longer be hidden. Historically, this condition was called "turban tumour" syndrome, reflecting the size the tumours reached if left unchecked.

Patients have voluntarily given me old family photographs, taken before their scalps were removed. Faded sepia conveyed lustrous curls and bright smiles. I think they did this because they wanted me to understand what this condition had done to them. It had robbed them of an important aspect of their femininity. The close bond I developed with the families fuelled my passion for the discovery of new, non-surgical, treatments.

To do this successfully in science sometimes requires a collaborative approach across several fields. An unorthodox combination of dermatologists, geneticists and a scientist who led a large breast cancer lab proved to be the right mix. The

synergy and exchange of ideas led to the development of my project that attracted funding from the Medical Research Council, who had the foresight to see this as an exciting tumour model that would also inform the understanding of other cancers.

With significant funding and backing, it was now feasible to look for new treatments with creative approaches. Unfortunately, little benefit was seen with aspirin. Returning to the drawing board, it was apparent that a better understanding of the tumours was needed. As I was already operating on these patients to remove painful and disfiguring tumours, I had an advantage – access to fresh tumour samples.

Using surplus tissue that would otherwise be incinerated, I carefully dissected out the tumour cells for analysis. The latest molecular techniques, that were *de rigueur* at the breast cancer lab I collaborated with, were now applied to a scalp tumour syndrome. Analysing the results was exciting. This showed that the tumour cells were using a defensive tactic that was making them resistant to programmed death, a process that normal cells in the body underwent. Surprisingly, this was a tactic that had already been discovered to be used by a completely different kind of tumour - a type of brain tumour. Promisingly however, this meant that drugs designed to overcome this advantage were already being developed.

The next step was to see if such drugs would actually be useful against the scalp tumour cells. Serendipity played a hand here. I was working with a biologist who had refined techniques to grow cells from hair follicles in the lab. She guided me to grow the tumour cells from surplus tumour tissue from the patients I had operated on. In this model, the brain tumour drugs were effective at killing off the scalp tumour cells at low concentrations that were already known to be safe in humans. When compared to aspirin, this drug was a thousand fold more potent. Encouraged by this, I am now in the process of taking this treatment towards a clinical trial.

Can we save her scalp? We are certainly a step closer. Furthermore the benefits may extend beyond the families who inherit this abnormal gene. It appears that the defensive tactic that gives the scalp tumour cells a growth advantage is also used by common skin cancers that affect millions of people. Pursuing the goal of non-surgical alternatives to scalp removal may offer new hope for patients who inherit this disease and also improve the understanding and treatment of skin cancer.



Max Perutz Essay Prize 2010: COMMENDED

Illuminating the Darkness

Sam Gibbons Frendo

Deep below the surface of the ocean, a monster lurks – a creature more at home in a science fiction film than here on earth. This strange quirk of evolution is the Anglerfish. Cruising through the ink black depths, the fish tempts its prey to their untimely end with a glowing lure that protrudes from its head.

If this peculiar method of finding a meal isn't fanciful enough, then consider for a moment that the glow from the fish's lure comes not from the fish itself, but rather from a colony of bioluminescent bacteria that have made it their home. The Anglerfish and its microscopic partners in crime live in a symbiotic relationship – each organism dependent upon the other for its own survival.

While we are pondering peculiar quirks of evolution, it should be noted that we owe our *own* existence to an ancient and vital symbiotic relationship. Way back in the history of life on earth, one single celled organism (in this case an ancestor of you and I) engulfed another. Call it fate or just some happy coincidence but this new 'double' cell did well. It did very well. The smaller cell became incorporated into its host and together they were able to perform cellular respiration – the breaking down of large molecules, like glucose, to release biochemical energy. These days we call these biological interlopers 'mitochondria'. Descendants of this strange union include every single plant and animal on the planet.

My PhD involves studying the way mitochondria behave inside neurons – the cells that make up our nervous system. Nearly all the cells in our bodies contain some mitochondria but neurons contain thousands. Think of them as the power house of the cell, burning fuel to keep the energy-hungry neuron up and running. The mitochondria are in a state of flux inside the cell, fusing and splitting and constantly shuttling to-and-fro. They do this to reach areas with high metabolic demand; these are places within the cell that need the most energy. The importance of these biological batteries means that if they start to malfunction, the consequences for the cell can be severe. And when neurons start to misbehave, the consequences for the body can be catastrophic.

Mitochondria play a role in a number of neurological disorders, ranging from Parkinson's to motor neuron disease. My research focuses on their role in Alzheimer's disease. Various findings suggest that changes in the way our brain uses energy is an early indication of impending Alzheimer's disease, occurring before any obvious memory loss. This means that mitochondrial dysfunction could be involved at an early and important stage of the disease. What's more, as cells age, mitochondria start to produce harmful chemicals that can damage other parts of the cell. Although it is a controversial theory, this harmful effect implicates mitochondria in the aging process itself.

But how can scientists see such tiny things moving inside cells? Molecular biologists have a trick up their sleeve to help them and they've turned back to the deep blue sea for inspiration...

The chances are you would miss the transparent jellyfish *Aequorea Victoria* if it wasn't for the fluorescent nodules that line the edge of its body. Luckily, at the beginning of the 1960s scientists spotted it and started studying the protein responsible for the fluorescent glow – suitably named 'green fluorescent protein' (GFP).

Three decades later our understanding had progressed to such an extent that it became possible to take the GFP gene and insert it into other organisms, like the humble bacteria *e.coli*. Critically, the protein functioned normally and made the bacteria glow. From this point on it became clear that GFP would be a vital tool for scientific research. Now we have the ability to manipulate GFP so precisely that it can be made to glow different colours. We can insert the gene into cultured nerve cells and use it as a tag to detect other proteins or, if we want, mitochondria.

This is how, as I stare down the eye piece of a microscope, it is possible to see glowing mitochondria emerging from the darkness. Instead of them being fixed to a microscope slide, their movement can be tracked around a living cell. Experiments can be performed to determine what effects their behaviour and why. GFP has enabled us to observe these cellular processes in real time, providing insights that would otherwise never have been known. My research will further our understanding of this behaviour and how it may be disturbed in Alzheimer's disease. By unravelling the mysteries of mitochondria we have a better chance of producing therapies to treat a host of devastating diseases.

The power this remarkable protein has given us would have been unimaginable when that first jellyfish was netted all those decades ago. Lucky the Anglerfish didn't get there first.