Access to Understanding

@EuropePMC_News
@ScienceBL
#A2UComp
Every year billions of pounds of public money are spent on scientific research. Both research funders and governments want to ensure that this research is read, understood and utilised by the widest possible audience. To achieve this aim, a group of European life sciences and biomedical research funders have developed Europe PubMed Central (Europe PMC), a free online life sciences and biomedical information resource.

However, providing online access to scientific information is only the first part of the story; enabling understanding is equally crucial. Much contemporary scientific information is currently accessible only to a niche audience because of its highly technical language, which can be intimidating to anyone outside a narrow scientific discipline. **Access to Understanding** is a new science-writing competition aimed at breaking down these barriers and encouraging PhD students and early career post-doctoral researchers to develop their skills in communicating cutting-edge research to non-specialists.

**Access to Understanding** also seeks to raise awareness amongst researchers of the increasing importance to the general public of being able to access and understand the outcomes of research that they pay for.

Competition entrants were asked to summarise a research article in a way that an interested member of the public would understand it. They were asked to explain the research and why it matters, in no more than 800 words. Nine articles were selected by Europe PMC funders, spanning basic through to clinical science that would be of interest to the public. The winning entry will be published by eLife; all short-listed entries are reproduced here. The original articles are all available from Europe PMC, are free to read and download, and were supported by one or more of the Europe PMC funders.

The competition is a partnership between Europe PMC and The British Library’s Science Team. The award ceremony is one of a series of events during The Library’s ‘Inspiringscience’ season, held to coincide with Brain Awareness Week and National Science & Engineering Week celebrations.

For more information and competition updates: [http://EuropePMC.org/ScienceWritingCompetition](http://EuropePMC.org/ScienceWritingCompetition)

**Europe PubMed Central** (Europe PMC) is a unique, free information resource for life sciences and biomedical researchers, backed by a growing number of European funders, who expect their supported researchers to make their published research available to the widest possible audience. It enables anyone with internet access to search and discover over 26 million abstracts and full-text articles from around the world.

Europe PMC was originally launched (as UKPMC) in January 2007, initially as a mirror of the US National Institute of Health’s PubMed Central (PMC), providing international preservation of open- and free-access biomedical literature. In 2010, the service diversified from PMC and introduced additional content including PubMed abstracts and biological patents, with innovations to improve navigation and search. Europe PMC now provides free access to:

- Over 2 million full text, peer-reviewed published journal articles
- Nearly 5 million biological and medical patents records
- More than 22 million PubMed abstracts
- Over 40,000 grants held by nearly 20,000 researchers.

Europe PMC is supported by 19 funders of life sciences and biomedical research, including charities and government organisations across the UK and Europe. The Europe PMC funders require that research papers funded by them must be made freely available via Europe PMC no later than 6 months after publication. The partner organizations delivering and developing Europe PMC are: the European Bioinformatics Institute, the University of Manchester, and The British Library.

Europe PMC engages with global users via social media and user demonstrations, as well as providing primary stakeholders with resources to interact with their own communities.

For more information, please contact the Europe PMC Engagement Manager, Anna Kinsey, at Engagement@EuropePMC.org

To access Europe PMC, visit: [http://EuropePMC.org](http://EuropePMC.org)

**Europe PMC funders:**
- Action on Hearing Loss
- Arthritis Research UK
- Austrian Science Fund
- Biotechnology and Biological Sciences Research Council
- Breakthrough Breast Cancer
- British Heart Foundation
- Cancer Research UK
- Chief Scientist Office of the Scottish Executive
- Dunhill Medical Trust
- European Research Council
- Marie Curie Cancer Care
- Medical Research Council
- Motor Neurone Disease Association
- Multiple Sclerosis Society
- Myovlytis Trust
- National Institute for Health Research
- Parkinson's UK
- Telethon Italy
- Wellcome Trust
The British Library

The British Library is the national library of the United Kingdom and one of the world’s greatest research libraries. It provides world class information services, both online and offline, to the academic, business, research and scientific communities and offers unparalleled access to the world’s largest and most comprehensive research collection.

Working directly with scientific researchers, funders and policy-makers, the Science Team at The British Library aims to support the information and data needs of research through an innovative programme of services, projects, events, and other activities. The British Library has helped to deliver Europe PMC, since its inception in 2006.

Access to Understanding was inspired by the Patients Participate project1, which asked “how can we open up research findings to everyone who is interested?” Patients told us they wanted easy-to-understand, evidence-based information relating to biomedical and health research, in the form of plain English summaries. Meanwhile, scientific researchers can find it challenging to communicate complex scientific information to the public in an accessible and engaging way. The project recommended publishing a lay summary alongside every [Europe PMC] article.

Access to Understanding is part of The Library’s “Inspiring Science” season of events and activities throughout March 2013. Inspiring Science will challenge, entertain and engage audiences, providing opportunities to debate, discuss, participate and learn how science can tell us about ourselves and the world around us.

Within this wider context, Access to Understanding aims to promote a dialogue between researchers and the public by enabling early career researchers to showcase their talents, and expand the reach of open access resources such as Europe PMC to make their contents truly understandable for all who are interested.

For more information on the Science Team’s activities, please contact Science@bl.uk.

For more information on Inspiring Science: http://www.bl.uk/inspiring-science

The key questions used to assess entries were:

- Does the entry explain the research accurately and in a way that is easy to understand?
- Does the entry explain why the research was done?
- Does the entry explain why the research is important?

There were two rounds of judging for the competition. Top entries for each research article were short-listed by Europe PMC funders and the Science Team at The British Library. Selection of the winning entries was conducted by our expert panel:

Janet Burke

Janet Burke is the Executive Director of eLife, a new open access journal for the biomedical and life sciences supported by the Wellcome Trust, the Max Planck Society and the Howard Hughes Medical Institute. As Features Editor she oversees the non-research content of eLife and also the eLife digests that are included in all research papers.

Simon Denegri

Simon Denegri is Chair of INVOLVE - the national advisory group for the promotion and support of public involvement in research funded by the National Institute of Health Research (NIHR) - and NIHR’s National Director for Public Participation and Engagement in Research. He also writes and speaks on issues concerning medical and health research policy and practice.

Sharmila Nebhrajani

Sharmila Nebhrajani is Chief Executive of the Association of Medical Research Charities (AMRC), a membership organisation of the leading medical and health research charities in the UK. The AMRC aims to support the sector’s effectiveness and advance medical research by developing best practice, providing information and guidance, improving public dialogue about research and science, and influencing government.

Peter Rodgers

Peter Rodgers is Features Editor at eLife, the new open access journal for the biomedical and life sciences supported by the Wellcome Trust, The Max Planck Society and the Howard Hughes Medical Institute. As Features Editor he oversees the non-research content of eLife and also the eLife digests that are included in all research papers.

Tracey Brown

Tracey Brown is Director of the charitable trust Sense about Science, which equips people to make sense of science and evidence on issues that matter to society. It promotes the principle of independent peer review and scientific enquiry free from stigma, intimidation and political pressure.

Stephen Curry

Stephen Curry is Professor of Structural Biology in the Faculty of Natural Sciences at Imperial College London. His research and teaching interests are combined with a passion for understanding the wider role of science in society using a variety of media — the written word, audio and video.

1 a partnership between The British Library, the Association of Medical Research Charities and UKOLN, funded by JISC
X-rays can now be used not only to show where bones have fractured, but also to investigate why these bones break in the first place. Results suggest the possibility of preventing the trauma of thousands of broken hips using drugs already commonly used for treating osteoporosis.

Normal healthy bones can be thought of as nature’s scaffold poles. The tightly packed minerals which make up the cortical bone form a sheath around an inner core of spongy bone and provide the strength which supports our bodies. Throughout our lives, our skeletons are kept strong by the continuous creation of new, fresh bone and the destruction of old, worn out bone. Unfortunately, as we age destruction becomes faster than creation, and so the cortical layer thins, causing the bone to weaken and break more easily. In severe cases, this is known as osteoporosis. As a result, simple trips or falls which only bruise a younger patient can cause serious fractures in the elderly. However, half of elderly patients admitted to hospital with a broken hip do not suffer from osteoporosis.

So why do those hips break? This is a question of great importance, as hip fractures are debilitating. Repairing one requires traumatic surgery that, even if successful, may not enable a patient to regain the full mobility they had beforehand. The National Osteoporosis Society estimates that 13,800 people in the UK die every year as a direct result of hip fractures. This is over 10% of patients injured. (http://www.nhs.uk/conditions/hip-fracture/Pages/introduction.aspx) Therefore, understanding how these fractures occur and acting to prevent them is vital for improving the quality and length of life of our ageing population.

To better understand why hips fracture, researchers in Cambridge and Prague analysed CT scans performed on the opposite, unbroken hips of a group of elderly women admitted to Bulovka University Hospital, Prague with hip fractures. Previous studies have shown that these tend to be in a similar condition to the broken hip pre-fracture.

CT scanners are now standard pieces of equipment in most hospitals, and are used to examine organs and tissues inside the body. Essentially a rotating X-ray machine, a CT scanner takes many X-ray snapshots at different angles around a body part to produce a 3D image of its internal structure. X-rays are energetic waves of energy which are partially absorbed by the materials they pass through. The amount of absorption depends on the density of the structure encountered – denser structures, like bone, absorb more of the X-ray energy, leaving less energy to be measured by the detector on the other side. However, the resolution of the images collected by a standard hospital CT scanner is not sensitive enough to accurately determine the thickness of the cortical bone.

A new image processing technique has changed this. Using it, the researchers in Prague and Cambridge were able to extract information from clinical CT scans that was sensitive enough to produce coloured maps on the surface of a model hip showing the variation of cortical bone thickness in more detail than ever. Variations in thickness of only 30 microns – the size of a grain of dust – could be detected.

The results were striking. Not only did the women with fractured hips have generally thinner cortical bone than normal, but some patients also had local patches of even thinner bone. This was the case even in women who did not suffer from osteoporosis. Most importantly, the extra-thin regions were found on the femoral neck – the part of the hip bone where fractures most commonly occur. In some patients, these patches were 30% thinner than the surrounding bone, and as big as a thumbnail. These weaker points provide the ideal conditions for a crack to form and subsequently grow into a fracture. Further studies are needed to confirm whether these localised regions do act as the starting point for a fracture, but at the very least they affect the type, and hence severity, of fracture which occurs. They could also explain the mystery of spontaneous hip fracture, which accounts for 6% of hip fractures – 4000 broken hips a year in the UK, which break for no known reason.

The research team have named these local patches of thinner bone ‘locally osteoporotic’. However, despite the name it is not yet known if these areas can be strengthened using standard osteoporosis drugs, which slow down the natural destruction of bone cells. An extensive clinical trial will be needed to investigate further, but if the focal patches do respond to treatment it raises the tantalising possibility of a future where many fractures could be treated before they even form. The improvement this would have on our quality of life in our old age would be invaluable.

1 “I have just stumbled across your science writing competition and I am extremely interested in this as an avid fan of public engagement activities.”

PhD student, UK

This article describes the research published in:

Cortical thickness mapping to identify focal osteoporosis in patients with hip fracture
Kenneth E. S. Poole, Graham M. Treece, Paul M. Mayhew, Jan Vaculík, Pavel Dungl, Martin Horák, Jan J. Štěpán, and Andrew H. Gee
PloS One (2012) 7(6), e38466
http://EuropePMC.org/articles/PMC3372523

This article was selected for inclusion in the competition by Arthritis Research UK

1 Quotes throughout are from individual researchers who provided feedback on what motivated them to get involved in the competition
Blood Vessels from Skin: The New Frontier in Tissue Engineering

By Ms Claire Sand
King’s College London, UK

For years scientists have attempted to harness the potential of stem cells for repairing damaged blood vessels. The tendency of stem cells to cause cancer, however, has meant that progress has been limited. Now, a team from King’s College London, led by Professor Qingbo Xu, have found a way of converting skin cells into blood vessel cells, raising hopes of new and improved treatments for cardiovascular disease.

Why is this research so important?
In an age where diets are rich in fat, cholesterol and salt, smoking is prolific and people are living to an increasingly old age, our blood vessels have never been more vulnerable. Damage to the inside of our arteries (in particular an important layer of cells called endothelial cells) can lead to coronary artery disease – the main cause of death in most industrialised countries. Consequently, scientists are striving to find ways of repairing or replacing damaged blood vessels with specially engineered tissues.

How are they doing this?
Traditionally, with stem cells. These have the ability to become any cell in the human body. During foetal development, embryonic stem cells take cues from the placental environment to become specialised heart or liver cells, for example. This process is known as differentiation.

The ability of stem cells to differentiate into any other cell has long been exploited by scientists, although ethical concerns and issues of immune rejection (where the body’s immune system attacks implanted cells) have seriously limited success. In 2006, a Japanese research group found a way of avoiding these issues by reprogramming (or de-differentiating) mature skin cells back into stem cells. These so-called induced pluripotent stem cells (iPS cells) could then be re-differentiated, using specialised conditions, into a different cell type altogether. This breakthrough raised the exciting possibility of ‘personalised therapy’. Skin cells from a patient with heart failure, for example, could be theoretically reprogrammed into heart cells that could be implanted without the risk of immune rejection.

So what’s the problem?
The main problem with iPS cells is that they can cause tumours. In order to make iPS cells, specific stem cell genes must be inserted into differentiated cells, forcing them to de-differentiate back into a stem state. Unlimited self-renewal is a key feature of stem cells, and introduction of stem cell genes into mature cells can cause them to multiply uncontrollably – just like tumour cells. Unfortunately, scientists have found that implantation of iPS cells causes cancer in a worrying number of lab mice.

What has Professor Xu’s group done differently?
De-differentiation of mature cells into iPS cells normally takes four weeks. Scientists in Professor Xu’s lab noticed that after only four days, skin cells lost their original characteristics without gaining those of a stem cell. Using specialised conditions the scientists were able to manipulate these partial iPS cells into becoming endothelial cells, which form the essential inner lining of blood vessels. Through this partial de-differentiation, they were able to eliminate the stem cell stage of reprogramming – and with it, the risk of tumour formation.

Are artificial endothelial cells the same as normal ones?
They have the same shape and size as endothelial cells, and contain the same unique genes. Importantly, they don’t have any of the characteristics specific to stem cells or the original skin cells, and can be used to generate artificial blood vessels in a biological simulator.

Crucially, the scientists had to test whether their endothelial cells can contribute to blood vessel repair in the body. They injected specially dyed cells into the legs of mice with artificially damaged arteries, and found that this greatly improved blood flow in the damaged legs. When the blood vessels were later dissected, the scientists found that they contained a high proportion of dyed cells. This suggests that the lab-made endothelial cells can combine with damaged tissues, and contribute to their repair. Importantly, none of the mice injected with these cells developed cancer in the time it normally takes tumours to appear.

Where will this lead?
In the relatively near future, lab-made cells and blood vessels will be a valuable resource for drug toxicity screening. Being of human origin, these cells and tissues are particularly relevant to human medicine, and could significantly reduce, if not replace, the use of lab animals for such testing. By using partially de-differentiated cells rather than stem cells, the scientists have also greatly reduced the time it takes to obtain viable endothelial cells, making the technique more practical to use in patients. ‘Personalised transplantation’ is still a long way off, and more safety assessments are needed. Nonetheless, in overcoming the problem of tumour formation, this team from King’s College London have brought blood vessel engineering one step further on the route from the lab to the clinic.

This article describes the research published in:
Direct reprogramming of fibroblasts into endothelial cells capable of angiogenesis and reendothelialization in tissue-engineered vessels
Andriana Margariti, Bernhard Winkler, Erimi Karamariti, Anna Zampetaki, Tsung-neng Tsai, Dilair Baban, Jannis Ragoussis, Yi Huang, Jing-Dong J. Han, Lingfang Zeng, Yanhua Hu, and Qingbo Xu Proc. Natl. Acad. Sci. USA (2012) 109(34), 13793-13798.
http://EuropePMC.org/articles/PMC3427074

This article was selected for inclusion in the competition by the British Heart Foundation

"Thank you very much for organising this. It’s great to see a big platform for biomedical science recognise the importance of science communication."
PhD student, UK
Another brick in the wall

By Mr Ian Le Guillou
University of Cambridge, UK

A mutation that allows cells to grow out of control could also provide a new way to target and destroy cancer cells. This potential Achilles’ heel comes from a mutation in a gene called PTEN, which is found in a wide range of cancers.

PTEN is one of many tumour suppressor genes that we have to prevent our cells from growing out of control. If the PTEN gene stops working because of a mutation, it can cause tumours to develop—indeed many tumours have a mutated form of PTEN. However, when a door closes, a window opens: the PTEN mutation helps the tumour to grow, but it could also mark it out as a target.

Researchers from the Institute of Cancer Research, London, found that switching off another gene known as NLK killed tumour cells that had the PTEN mutation. This makes NLK a good target for drug developers to create a new cancer treatment.

The difficult thing about cancer is that it is made of us—our own cells mutate and grow wildly out of control. That means it is unlikely there will ever be a quick fix. Antibiotics work efficiently because bacteria are so different to us that we can develop drugs that target their weaknesses yet barely affect our own cells. But how do you kill something that is the same as you? Current treatments for cancer cause a lot of side-effects in patients because as they try to kill the cancer they also do damage everything else in the body. This is why finding ways to target cancer specifically is so important.

There are several proteins in our cells which we cannot live without, and if the genes responsible for producing those proteins are mutated or switched off the cells die. Targeting these proteins and genes are rarely going to be useful for treatments, as they will kill the patient about as quickly as they kill the cancer. So Alan Ashworth and colleagues set out to find proteins that are not essential in healthy cells, but cells with the PTEN mutation cannot live without. This would pave the way for designing drugs that target the tumour and leave healthy cells alone.

The researchers took samples of tumour cells with and without the mutation, and switched off genes for important proteins that are used for regulating lots of processes in the cell. To do this they used small molecules of RNA (DNA’s less famous cousin) which interfere with the processes of specific genes. This is why these molecules are known as small interfering RNA (or siRNA). They block the chain of events why these molecules are known as small interfering RNA (or siRNA). They block the chain of events that allow a gene to produce a protein, effectively switching it off. By switching off 779 genes individually, they could look for ones where cells with the PTEN mutation died and cells without the mutation survived.

This is how the researchers discovered the powerful effect of switching off the NLK gene. They are not certain how this works but it appears to protect a protein called FOXO1 that can act as a backup tumour suppressor and cause the cancer cell to die. When PTEN is mutated, the FOXO1 protein becomes vulnerable to a process called phosphorylation, which means it is ejected from the cell nucleus and destroyed. NLK is one of the proteins that phosphorylates FOXO1 and so by switching off the NLK gene, FOXO1 is able to do its job.

This is just the start of a long journey from the lab to (potentially) the hospital. The researchers have shown that targeting NLK is more likely to kill mutated cells than normal cells, but that does not mean it is safe. NLK still has a role to play in healthy cells and preventing it from working is likely to have side-effects, but it could be worthwhile if this approach can kill tumours. The next stage is to develop a drug to stop the NLK protein from working, so that it can be tested further in cells and in living organisms.

Promising leads against cancer appear often, yet very few ever make it as treatments. One big hurdle is making it through clinical trials; the new drug has to be better than currently available treatments. Targeting NLK would only work against cancers with the PTEN mutation, but now we can use the mutation as a marker to find out which patients it applies to. We are now in the age of personalised medicine, where we can have 100 different treatments for 100 different people with 100 different cancers. Gradually, we are finding ways to attack cancer in whichever form it appears and build up our range of treatments. The weaknesses that we find are not going to cure all cancers but each one provides another brick in the wall.

This article describes the research published in:

NLK is a novel therapeutic target for PTEN deficient tumour cells
Ana M. Mendes-Pereira, Christopher J. Lord, and Alan Ashworth
PLoS One (2012) 7(10) e47249
http://EuropePMC.org/articles/PMC3483146

This article was selected for inclusion in the competition by Breakthrough Breast Cancer
Genetic study reveals that a significant proportion of intelligence is inherited

By Mr Robert Hoskin
University of Sheffield, UK

To what extent do biological and environmental factors influence how an organism develops? This question, often framed as the ‘nature-nurture debate’, is one of the most fundamental problems that science has to address. Within this debate it is of particular importance to understand how biological and environmental factors contribute to the development of human intelligence, as intelligence plays a substantial role in determining life outcomes. A 2011 study, published in the Molecular Psychiatry journal, has demonstrated that differences in adult intelligence can, to a large extent, be explained by genetic variations between people. The study therefore provides clear evidence that a significant proportion of adult intelligence is hereditary.

The research was the result of wide-scale collaboration between scientists at 8 different universities, across 3 different countries. They analysed DNA collected from over 3000 unrelated volunteers. Each individual’s DNA was scanned for the presence of a large number of common genetic variations (known as single-nucleotide polymorphisms or ‘SNPs’). These genetic variations effectively encode the biological differences between people. Their study can therefore reveal the genetic basis of individual differences. For example, if a particular gene has a causal effect on a trait (in this case intelligence) then individuals with an SNP within that gene should have noticeably different scores on the trait compared to those who do not. Measures of each individual’s intelligence were ascertained from various psychometric test scores collected from each volunteer during middle to late adulthood. Two separate measures of adult intelligence were computed: a measure of cognitive skills such as abstract reasoning, logical thinking and problem solving.

The research team were not able to establish a firm relationship between any individual SNP and either measure of intelligence. One SNP (named FNBP1L) was found to predict fluid intelligence, but this relationship could not be replicated using an independent sample of data from Norway, suggesting that the effect may be spurious. The identification of SNPs also however enables a genetic profile of each individual to be created, a process which in effect allows the cumulative genetic variation between individuals to be quantified. These profiles therefore allow an assessment to be made of the extent to which more general variations in genetic makeup contribute to individual differences. Using this method the researchers found that 40% of the variance in crystallised intelligence and 51% of the variance in fluid intelligence between individuals could be explained by genetic differences. Furthermore the predictive information contained within the SNP profile was also able to predict intelligence scores in the independent Norwegian dataset, confirming the validity of the original finding. These results strongly suggest that around half the variation in intelligence between people can be attributed to inherited abilities. Indeed as only common SNPs were analysed, rather than every single genetic variation, the actual proportion of intelligence that is heritable may be much higher than this.

The estimates regarding the heritability of intelligence provided by the study are in broad agreement with those obtained from twin and family studies. This study however strengthens our understanding of the heritability of intelligence because it side-steps some methodological issues that exist with twin and family studies, such as the difficulty in parsing genetic from environmental influences when closely related individuals are studied. The study therefore represents the first direct demonstration that genetic differences explain a significant amount of the variance in intelligence between individuals.

As no individual SNPs were found that strongly predicted intelligence, an additional conclusion that can be drawn from the study is that a very large number of different genes are likely to interact to determine our intelligence, rather than there being a small number of ‘intelligence genes’. This is perhaps not surprising as intelligence is a complex trait that is reliant on a number of different cognitive abilities, which are in turn likely to be reliant on a number of different biological processes. The likely influence of a large number of genes does not suggest that associations between individual SNPs and intelligence cannot be uncovered in the future. Instead it suggests that studies with far larger samples, and perhaps looking at more specific cognitive abilities, will be required in order to identify such associations. Nevertheless the study represents an important step in the battle to understand the genetic basis of intelligence. By improving our understanding of the biological mechanisms that support intelligence we may be able in the future to identify ways in which the development and maintenance of human mental functioning can be improved. This may lead to interventions that can help to both promote cognitive abilities in the general population, and preserve these abilities to a greater extent in old age.

This article was selected for inclusion in the competition by the Biotechnology and Biological Sciences Research Council.

“ Many thanks for providing such a fantastic opportunity. I have learnt a great deal about a completely new topic.”

PhD student, UK

---

This article describes the research published in: Genome-wide association studies establish that human intelligence is highly heritable and polygenic


Mol. Psychiatry (2011) 16(10), 996-1005
http://EuropePMC.org/articles/PMC3182557

---

---

---

---

---
Oestrogen is a female hormone, produced in the ovaries, that stimulates the formation of the female sexual characteristics at puberty. It also triggers the growth of the breast tissues during the reproductive cycle and during pregnancy. However, oestrogen exposure in a woman’s lifetime has been linked to breast cancer risk for many years. During the development of breast cancer, oestrogen feeds the breast tissues and the tumour indolently and consequently helps its progression. Treatments that block oestrogen receptors have been successfully used in the clinic, however the response is difficult to predict and some patients eventually develop resistance to those drugs. Understanding how oestrogen and its receptor work is key to developing new effective therapies against breast cancer.

Scientists at Cancer Research UK in Cambridge have discovered that the oestrogen receptor (ER) activates a different set of genes in breast cancer patients who died compared to patients who survived. This important study could help scientists understand why a disease that appears superficially identical, has such differing outcomes in terms of response to treatment and, ultimately, survival.

ER belongs to the family of transcription factors, which means that it can travel to the cell nucleus, when partnered with oestrogen, and reach the DNA molecules that harbour all our genes. Like all transcription factors, ER has the capacity to attach to some specific "target" genes, and lead to their activation or inhibition, which will in turn tell the cells how to behave. ER is aided in reaching its nuclear targets by the pathfinder transcription factor FOXA1, which opens up the DNA molecule for easy access. It is known that this collaboration between ER and FOXA1 involves many genes and is very dynamic, but the importance of its role in cancer development is still unclear.

Using molecular biology tools, scientists can “capture” a transcription factor together with the DNA to which it is bound. It is then possible to read the DNA sequence obtained from these binding events in order to identify target genes of specific transcription factors. This technique, previously used in cancer cell line models, was applied for the first time by the team in Cambridge to biopsies from breast cancer patients that all possessed ER and FOXA1. These patients were carefully chosen according to how aggressive their cancer was: eight patients with good prognosis, seven patients with bad prognosis and three who had a relapse and developed metastases were selected.

The team identified the target genes of ER and compared them between the different groups. The results showed that 484 binding sites (i.e. spots on the DNA where ER is bound) were common to most of the patients, but that the strength of the binding was more important in poor outcome and relapse patients compared to good outcome ones. The experiment also indicated that the different outcome patients can be well characterised by a specific set of ER bound genes: 1,192 binding sites were predominantly found in the poor prognosis group and another, distinct 599 binding sites were representative of the good outcomes. The authors also observed that the pathfinder FOXA1 was more often binding near the poor outcome ER binding sites than the good ones.

The experiments revealed that ER was responsible for a double whammy; activating the poor outcome genes but also inhibiting the genes in the good outcome group, meaning that the binding of ER at those specific binding sites was biologically relevant in term of regulating cell behaviour.

In order to validate these finding they turned to well established cancer cell line models that were either drug sensitive or drug resistant, reproducing what is seen in patients. However, contrary to what they had hypothesised, the drug sensitive cell model was more similar to the poor outcome patients group, in term of ER binding sites, possibly suggesting that these models constitute an intermediate category of tumours, with an ER binding profile resembling more advanced tumours, on their way to acquired drug resistance. The events that led to this intermediate category might have been caused by the presence of other stimuli, such as other hormones or growth factors for instance, in the patients from whom the cell line models were established. By treating drug sensitive cells with some of these chemical stimuli, they were able to shift the ER binding profile, and observed an increase in new FOXA1 binding sites.

We have known for many years that ER can play a critical role in orchestrating the behaviour of breast cancer cells, but the emergence of FOXA1 as the principal conductor sets the stage for novel approaches in targeted therapy.

---

**Breast Cancer: Two-face ER**

By Miss Luisa Robbez-Masson

Barts Cancer Institute, Queen Mary, University of London, UK

---

"I find that I enjoy talking about mine or others research to non-scientific friends and family and believe it is very important that we can present our work and findings to the wider public, thus saw this competition as an excellent opportunity to take part in such a dialogue."

PhD student, UK

---

This article describes the research published in: **Differential oestrogen receptor binding is associated with clinical outcome in breast cancer**


Nature (2012) 481(7381), 389-393

http://EuropePMC.org/articles/PMC3272464

This article was selected for inclusion in the competition by Cancer Research UK
What are integrins?
Integrins are crucial proteins in cell migration, because they are integrated into the cell membrane and are responsible for cells attaching to surfaces, a kind of molecular ‘glue’. Their important role is to integrate, thus the name, the inside of the cell (cytoskeleton) to the outside (ECM and other cells). Integrins get cues about the environment and distribute the information in the cell, so that the cell knows how to behave and can respond accordingly. It is not surprising then that the levels and activities of integrins change in many types of cancer, and help to promote cell migration or metastasis.

How can normal cells mimic metastatic cancer?
Integrins can be influenced by other proteins. In this new study, the researchers focused on Fam38A, which helps to switch on the integrins. They showed that Fam38A is found at high levels in normal lung cells but it is almost absent in small cell lung cancer cells. To discover if this is important in driving lung cancer metastasis, they ‘silenced’ the expression of this protein in normal cells, so that its level was similar to that in cancerous cells. They found that when Fam38A is almost missing, integrins become inactive, and the cells stop adhering to their surroundings as readily as normal cells. Surprisingly, the cells missing Fam38A were also shown to eagerly move around and to be more invasive than normal lung cells.

The next question to ask is how is this possible? How can the cells migrate, when levels of active integrins are low, and cells need integrins to adhere at least in some types of migration? The exciting answer is that their movement no longer depends on integrins. The cells can switch to so-called amoeboid migration, when they move similarly to free-living single celled organisms called amoeba. Amoeboid migration is known to be often used by various cancer types, including small cell lung cancer.

What does this mean for the patients?
This intriguing discovery shows that the loss of one humble protein causes a fundamental change in cell behaviour. It has such drastic consequences for cell migration, Fam38A is likely to be very important for lung cancer metastasis. For example, detecting low levels of Fam38A in tumours during screening is likely to mean that the cancer has higher potential to become aggressive and metastatic.

Further studies seem necessary before this finding can be applied clinically. Nevertheless, it certainly helps to unveil the mechanisms behind cancer metastasis and hopefully will contribute to discovering new therapies for lung cancer in the future.
Pregnancy complications expose future disease risk

By Dr Gráinne Long
MRC Epidemiology Unit, Cambridge, UK

Cardiovascular disease (CVD) describes any disease that affects the heart or blood vessels, and is currently the leading cause of death in women world-wide. Now complications during pregnancy can be used as an early indicator to identify women at high risk of future cardiovascular disease. Pregnancy provides a window into early adult female health, which can flag women at high risk of future ill health and may allow treatments to be targeted early to those who need it most. In this way CVD could be delayed or even prevented, suggest researchers who have looked at the relationship between pregnancy complications and future disease.

Earlier studies support a link between common complications during pregnancy and increased risk of CVD in later life. Women with a history of pregnancy related diabetes or pregnancy hypertension, pre-term delivery (i.e. before 37 weeks), or those bearing a low or high birth weight child, are more likely to develop future CVD. But whether these four complications independently predict risk of future disease, or whether one or a combination of pregnancy complications are better predictors of future health is unclear. For example, are a mother’s chances of developing future heart disease best predicted by a history of a specific complication, say pregnancy diabetes, or by a combination of complications, such as pregnancy diabetes and hypertension? This is important to figure out in order to establish whether similar pathways to CVD exist, which may provide opportunities to treat and stop disease.

Paths to disease
Debbie Lawlor and colleagues at the University of Bristol and University of Glasgow got around these pitfalls by studying the effects of all four pregnancy complications together on a range of CVD risk factors. CVD risk factors are known indicators of future increased CVD risk and include high blood glucose, insulin and fatty materials. Lawlor’s team looked at the pregnancy history of a large population of 3,416 mothers who also had key CVD risk factors measured an average of 18 years after pregnancy.

Using statistical tools, a range of factors, or confounders, that could be alternative explanations for the link between pregnancy complications and CVD risk were also taken into account by Lawlor’s team; namely smoking, a mother’s education level and body mass. For example, smoking during pregnancy can increase CVD risk and also lead to a low birth weight child. So, taking smoking and other important confounders into account, allows true associations to be separated from those that are false.

Of the four pregnancy complications examined, pregnancy diabetes and hypertension were the best independent predictors of future CVD risk. Mothers with a history of pregnancy diabetes, were more likely to have raised blood glucose and insulin compared to healthy mothers some 18 years after pregnancy. Women with a history of pregnancy hypertension had a higher chance of having increased insulin and unhealthy fat (cholesterol and triglycerides) later in life, compared to their healthy counterparts. These associations did not change when statistical tools took account of all pregnancy complications and important confounders together, suggesting both pregnancy diabetes and hypertension are independent risk factors for CVD.

What about the effect of pregnancy complications on future CVD, rather than simply CVD risk factor levels? As the actual rate of CVD in this population was low, reflecting the relatively young age of the women, a well known ‘scoring system’ was used to estimate future CVD risk based on all the measured CVD risk factors combined. Using this approach Lawlor’s team found that, compared to healthy women, those suffering from pregnancy diabetes or pregnancy hypertension are 23% and 27% more likely to have a CVD event in the next 10 years, respectively. These findings held even when all pregnancy complications and confounders were taken into account together, further supporting a role for both complications as important predictors of future CVD risk.

Pregnant promises
“The stress test of pregnancy provides a glimpse into the otherwise silent early adult years in which chronic disease trajectories are set.”, says Ellen Seely1 who specialises in cardiovascular diseases in women at Harvard. She says further investigation into the contribution of pregnancy complications to CVD is needed to fully understand, and benefit from, the early warning system pregnancy provides for predicting future health. Opportunities to screen during pregnancy and intervene in high risk women early to slow or stop disease progression could be on the horizon.

“ It is great that you are helping scientists participate in science writing. ”
Post-doctoral researcher, France

This article was selected for inclusion in the competition by the Medical Research Council

http://EuropePMC.org/articles/PMC2948753

http://EuropePMC.org/articles/PMC3323835

Circulation (2012) 126(11), 1367–1380
http://EuropePMC.org/articles/PMC3323835

This article describes the research published in:
with calculated CVD risk and cardiovascular risk factors in middle age: The Avon Longitudinal Study of Parents and Children
Abigail Fraser, Scott M. Nelson, Corrie Macdonald-Whites, Lynne Cherry, Elaine Butler, Naveed Sattar, and Debbie A. Lawlor

19
How do nerve cells die?

Many human diseases involve degeneration of the nervous system – a system of interconnecting nerve cells, allowing us to sense and respond to our environment. All of these disorders are incurable and fatal. Most of them share a common feature – aggregation of abnormal protein within nerve cells. One such protein is TDP-43 which accumulates in some dementias and disorders that affect motor neurons – the nerve cells that tell our muscles to contract. In a small number of families, motor neuron disease is inherited because the gene that produces TDP-43 is faulty. This confirms that TDP-43 is important in the disease process. It does not explain how changes in this protein cause nerve cell death.

Disease models, using animals or generic cells in a dish, do not mirror the human condition and need artificially increased protein levels to show an effect. To overcome these issues, the researchers in this study used a cutting-edge technique. It is now possible to take a skin sample from a patient, place the skin cells in a dish, and “re-program” them into stem cells. Stem cells can become any cell type in the body. They can be multiplied and “instructed” to make motor neurons by exposing them to a few agents. If the donor patient has a faulty TDP-43 gene, all the neurons made from that patient’s skin will have faulty TDP-43 – the nerve cells that tell our muscles to contract. In a small number of families, motor neuron disease is inherited because the gene that produces TDP-43 is faulty. This confirms that TDP-43 is important in the disease process. It does not explain how changes in this protein cause nerve cell death.

Testing the kit

First, the researchers checked the reprogramming had worked, and that the faulty gene was present in the stem cells made from the patient. They confirmed that motor neurons could be generated from all samples by showing they contained a specific combination of proteins. Mature nerve cells carry electrical messages, which they transform into chemical messages to communicate with other cells. Electrical messages are created when “gates” in the membrane surrounding the cell are opened and closed. The gates control the movement of charged particles into and out of the cell. Different gates permit passage of different particles, thus producing different messages. The messages can be recorded whilst blocking each type of gate in turn. In this way, the investigators demonstrated that all of the nerve cells were equipped with motor neuron gates. The gates were operating correctly.

So the faulty gene did not affect the maturation and basic function of the neurons in this study. It did however cause an increase in the level of TDP-43 protein within the cells, and some of this protein was abnormal. All proteins have natural ‘shell-life’; old proteins must be degraded and replaced with new ones. The workers showed that the healthy and diseased neurons were producing the same amount of TDP-43. This suggested a problem of waste-disposal; either the cell recycling machinery was impaired, or it could not break down abnormal TDP-43. The faulty neurons were also nearly four times more likely to die than the healthy neurons. When a survival system within the neurons was inhibited, the healthy neurons coped better than the diseased ones. Together these findings indicated that the patient neurons were more fragile, because they contained abnormal and increased amounts of TDP-43.

An answer in the palm of your hand

Like baking bread, just four ingredients are needed to turn skin cells into stem cells. This stem cell ‘dough’ can be moulded into any cell type of choice, for any body system (e.g. the nervous system). A few more ingredients give these cells a regional identity within that body system (e.g. motor neuron). In the right environment, cells will develop a ‘native language’ so they can interact with their neighbours and perform the roles expected of them, within their cellular community. The motor neurons here had all the tools to carry out their function, but they lacked material to work on (i.e. muscle). The techniques above could be used to make muscle cells and grow them with motor neurons – the dough can always be remoulded.

Although samples came from only one patient, this paper proves that some aspects of this patient’s disease can be modelled in a dish. This concept could be extended to any other disease resulting from a faulty gene. By comparing patient samples with those from people with a normal version of the gene we can understand better how the disease develops. There are many ways in which one abnormal protein might lead to cell death – consider the endless routes that could get you from one station to another on the underground. But every route offers a further opportunity to intercept, delay, or reverse the disease process. If we discover how to treat the disease in a dish, we can make headway in treating the patient.
Most people may not think very much about reasons explaining the shape of our feet. For evolutionary biologists and designers of prosthetic legs however, this topic is of major interest. A recent study, led by Dr James Usherwood from the Royal Veterinary College in England, provides new evidence that our feet are specifically designed for walking.

To understand why however, requires a brief overview of human walking 101. Just as people dance with certain styles, we also walk with a certain style. This movement is no hokey-poky, however. Rather, scientists call our walk the inverted pendulum. Inverted pendulums are characterized by objects that move in an arching, rainbow-like fashion overtop of a fixed pivot. A catapult exemplifies an inverted pendulum. Likewise, while walking our bodies act as a weighted object that propels forward over our feet, which serves as a fixed pivot. Imagine the way a wiper blade moves across a car windshield. Such is the motion made by both walking people and inverted pendulums.

Yet, this confusing concept may be best grasped while actually walking. So, let’s do the inverted pendulum (imagine beat of “the hokey pokey”).

We put one foot out, and place the heel down.
We pivot further forward, lifting our heel and using the toes to push off into the next step.

That is what the inverted pendulum is all about.

What has specifically confused scientists is why humans are flat-footed, with heels that touch the ground while walking and standing. As ostriches illustrate, such a foot is not essential for doing the inverted pendulum. These large, flightless birds known for running at impressively high speeds use the inverted pendulum style to walk as well, but their heels are always elevated off the ground. Furthermore, women in high heels still do the inverted pendulum as well. Thus, the ground-touching heel is inessential. Moreover, ostrich feet may actually be preferred, as the need to spend energy lifting the heel off the ground is eliminated.

What these past studies fail to consider however, is the burden that walking places on the leg muscles. Therefore, James Usherwood, from the Royal Veterinary College in the United Kingdom, and colleagues examined muscle use throughout the inverted pendulum walk, to see whether any insights into the function of the heel could be afforded. They did this by first breaking down the inverted pendulum into 3 steps. In Step 1 we place our heel down on the ground.

Arriving overtop we stand with bodies and legs erect.
We pivot further forward, lifting our heel and using the toes to push off into the next step.

The human foot and heel–sole–toe walking strategy: a mechanism enabling an inverted pendular gait with low isometric muscle force?

J. R. Soc. Interface (2012) 9(75), 2396–2402
http://EuropePMC.org/articles/PMC3427509

This article was selected for inclusion in the competition by the Wellcome Trust.

Published by the Royal Veterinary College

This article describes the research published in:

“Thank you for organising this competition as it has been an eye-opening exercise on how easily scientists get carried away with jargon.”

Post-doctoral researcher, UK