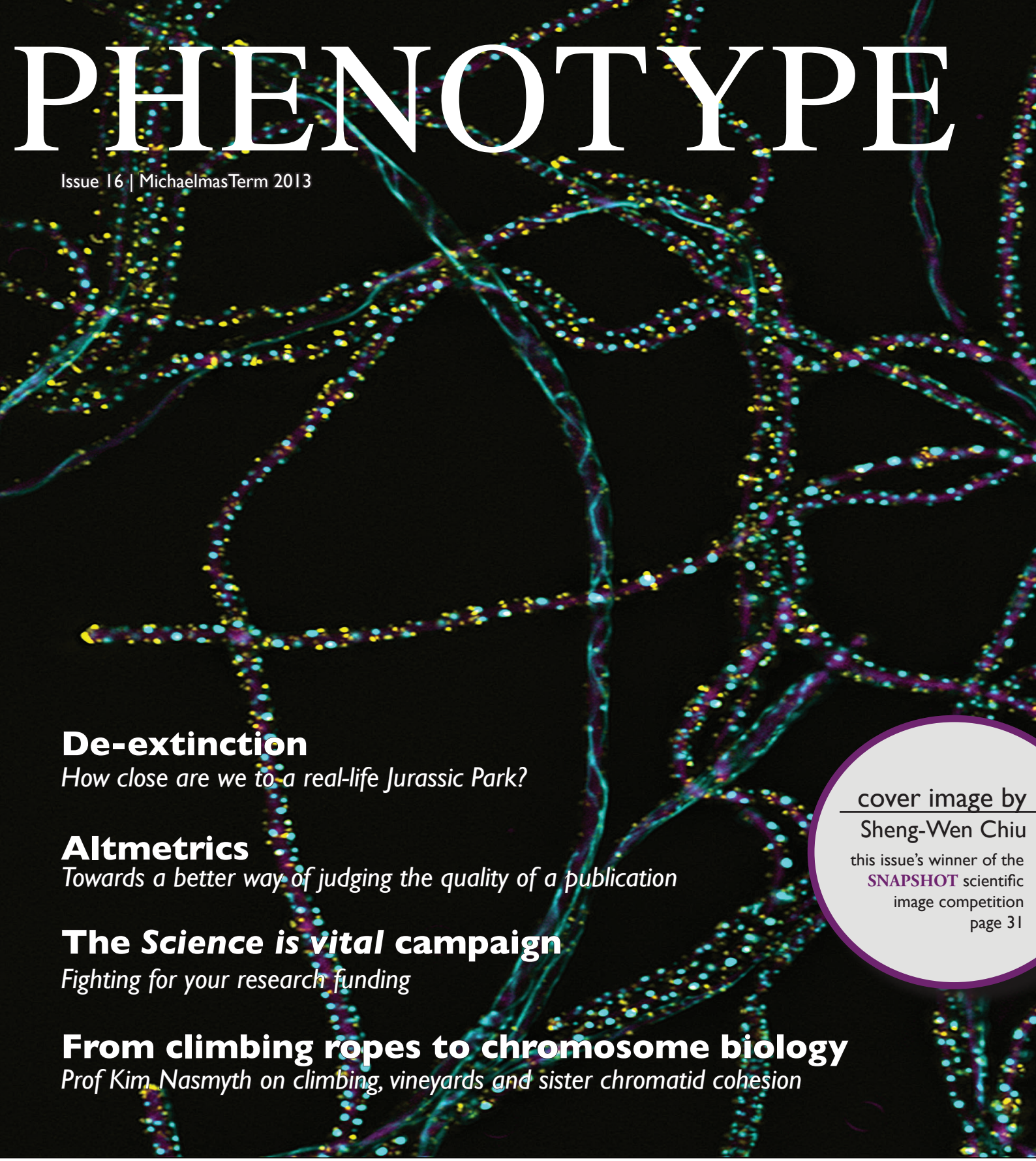
PHENOTYPE

Issue 16 | MichaelmasTerm 2013



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Fighting for your research funding

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Sheng-Wen Chiu
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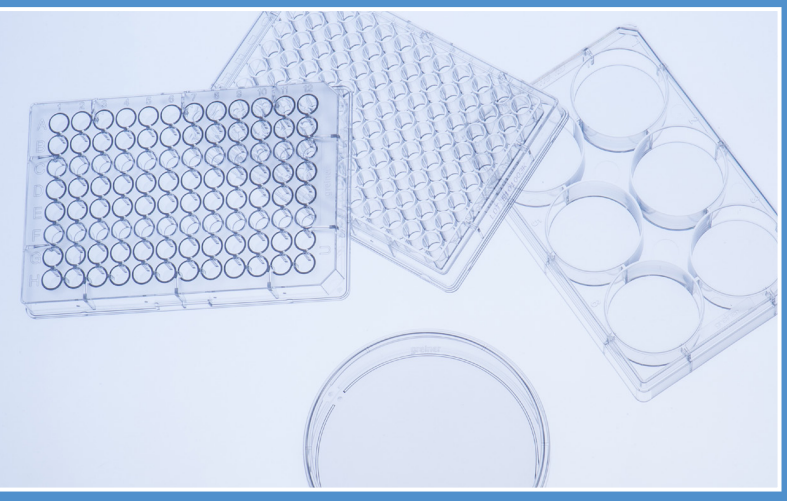

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EDITORIAL

Welcome to the sixteenth issue of *Phenotype*! I hope you will enjoy reading the varied and exciting articles contributed by PIs, research staff and students from across the University.

In our PI article 'with a twist', Prof Kim Nasmyth from the Department of Biochemistry introduces us to his extra-curricular activities, climbing and running a vineyard in southern France, explaining how they have helped him to understand how the cohesin complex is able to hold DNA sister chromatids together, and also why having a broad range of interests in addition to your science is important for coping with problems in the lab. We also feature an interview with Prof Scott Waddell from the Centre for Neural Circuits and Behaviour, in which he reveals the best advice he has ever received and his favourite classical experiment.

This issue we also highlight science communication and publishing. Dr Elizabeth Hartfield investigates why scientists struggle with something as omnipresent as communication and gives useful tips on how to improve your communication skills. Guest author Iain Hrynaszkiewicz from Faculty of 1000 explains why the impact factor of a journal is usually not the best way to rate the quality of a paper and introduces 'altmetrics', alternative methods to judge the impact of publications.

In our other features, Rupal Mistry is trying to find out if *Jurassic Park* could become reality by examining the current techniques in place to clone extinct animals (no dinosaurs yet, I'm afraid!), and Hayley Tyrer reports on the cancer drug Glivec and the patent issues that big pharmaceutical companies currently face in India.And if you've wondered how to set up a company yourself, read the roadmap to success of Puridify, the winner of the OneStart biotech competition, by Jenny Dvorzak. On page 14, Hannah Buxton discusses the evolution of theories explaining autism and examines how the autism triad of symptoms – impaired communication, poor social reciprocity and restricted interests – has hindered the full understanding, and hence treatment, of the disease.

In our science and society section, Dr David Yadin reports on the *Science is Vital* campaign launched in 2010, which fights to improve science funding in the UK. In an essay inspired by Angelina Jolie, Andrew Douglas comments on her choice to undergo elective mastectomy due to her breast cancer disposition, as well as on her decision to go public with it.

This term, OUBS will be hosting Prof Ben Lehner. Find out more about his research from Dr Daian Cheng, who tells us why it is not straightforward to predict the phenotype of a given genotype.

Congratulations to DPhil student Sheng-Wen Chiu, the winner of last issue's **SNAPSHOT** competition, who imaged chemosensory protein clusters together with cytoskeletal proteins in *Rhodobacter sphaeroides* using 3D fluorescence deconvolution microscopy. To find out more about his work and the image please turn to page 31.

If you like cryptic crosswords, try your hand at cracking our cryptic molecular biology crossword by our new cryptographer *Fish* on page 32. The lucky winner will receive one of the Wiley-Blackwell textbooks reviewed this issue. For those of you who are still wondering what *5 down* from last issue's crossword is, the answers are available on the same page.

I have thoroughly enjoyed my term as editor and encourage anyone interested in science communication, writing and publishing to join the *Phenotype* team. Writers, editors, designers: please get in touch if you are interested in science journalism, or in any aspect of its production. Or why not join the sponsorship team? Contact us at **oubs@bioch.ox.ac.uk**!

Finally, thank you to the motivated, dedicated and creative *Phenotype* team of post-docs and students. Your hard work and enthusiasm can be found on every page of this wonderful issue of *Phenotype*.

Johanna Scheinost
Editor

OXFORD UNIVERSITY BIOCHEMICAL SOCIETY

Phenotype is also available online: www.bioch.ox.ac.uk/oubs/phenotype.php

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OUBS SEMINARS

All seminars are held in the Main Meeting Room, New Biochemistry Building from 4 to 5 pm, unless stated otherwise.

Featured Seminar

Monday 2 December

Prof Ben Lehner, *Centre for Genomic Regulation, Barcelona, Spain*

For a full list of the Monday seminars, please check the OUBS website: http://www.biochem.ox.ac.uk/oubs/

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OUBS Featured Seminar: Prof Ben Lehner

by Dr Daian Cheng

This term, the Oxford University Biochemical Society (OUBS) brings you Prof Ben Lehner from the Centre for Genomic Regulation (CRG), Barcelona, Spain.

Lehner's group studies the complex question of how gene mutations are translated, or not, into particular phenotypes (1, 2) and investigates the principles of how individuals are affected by their genomic sequences. It was the groundbreaking work of the Human Genome Project that first drew Lehner to a career in genetic research. He obtained a PhD from the University of Cambridge and completed post-doctoral research at the Wellcome Trust Sanger Institute, before moving to Barcelona's CRG. Lehner's research has led to an impressive list of publications and awards, including the 2013 Eppendorf Award for Young European Investigators for his outstanding contributions and original approaches in biomedical research.

One of his key findings is that individuals with identical genes do not necessarily have identical phenotypes, and that this could mean health or disease, or even life or death. For example, in a batch of *C. elegans* with a null mutation in the T-box transcription factor gene *tbx-9*, around 50% of the worms hatched with abnormal morphology, whereas the other half were phenotypically normal (3). The cause for this difference in morphology was not genetic, nor was it environmental, so what is going on?

Thanks to various studies, we now know that the interplay between a number of genes is an important factor in the emergence of a phenotype. The effect of a mutated gene is very much dependent on small variations in expression of other genes in the early stages of development (Figure 1). In the *C. elegans* example, the different outcomes of the null *tbx-9* gene were shown to depend on the expression levels of two other genes, *tbx-8* and *daf-21*. *Tbx-8* is an ancestral gene duplication of *tbx-9*, and the removal of either *tbx-9* or *tbx-8* alone caused similar incomplete exhibition of phenotypes, whereas removing both simultaneously resulted in synthetic lethality. Using a GFP reporter assay, Lehner and colleagues observed elevated expression of *tbx-8* in the embryos with a null *tbx-9* mutation and *vice versa*, indicating the presence of a compensatory feedback mechanism. The level of *tbx-8* induction correlated with the phenotypic outcome, with higher expression of *tbx-8* leading to an increased probability of normal morphology. *Daf-21*, an Hsp90 chaperone, was also expressed at higher levels in worms that hatched normally. A striking 92% of the *tbx-9*-null embryos that expressed above average levels of both *tbx-8* and *daf-21* hatched without abnormalities.

These results demonstrated that with a good understanding of the relevant genetic interactions and a good readout of expression levels, the effects of a given mutation can be more accurately predicted. Such genetic interactions might involve ancestrally duplicated genes such as *tbx-9* and *tbx-8*, or genes that are involved in the same pathway or are co-expressed.

The use of simpler models, such as bacteria, yeast and worms, allows the use of large-scale systematic screens, and thus genetic and environmental manipulations are easily controlled. Furthermore, there is often a more direct relationship between genotype and phenotype in these organisms. Although the actual mechanisms and pathways of diseases in these organisms are different from those in humans, regulatory principles tend to be evolutionarily conserved.

Individual patients do not want to know the possible outcomes of mutations that they carry; they want to know what will actually happen to them. The research carried out by Lehner's group on the biology of individuals therefore provides important steps towards the realisation of personalised and predictive medicine.

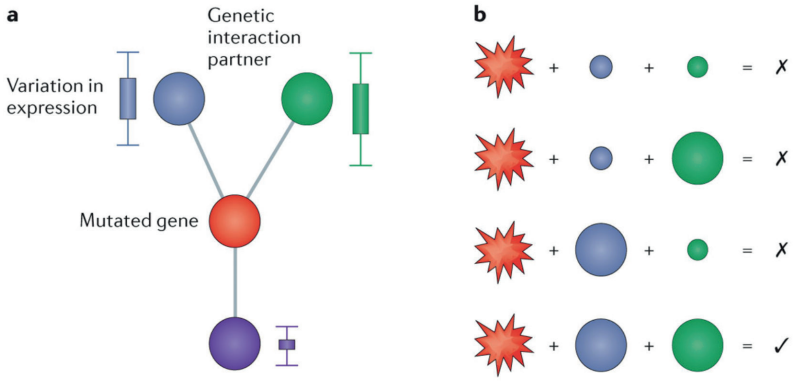

Figure 1: (a) A phenotype directed by a mutated gene (red circle) may be enhanced either by mutations in partner genes (blue, green, purple circles), or by variation in the expression level of these partners (indicated by box plots next to each gene). (b) One scenario showing how the outcome of a given mutation (red) depends on expression levels of related genes (blue, green). Reprinted with permission from (1).

References

1. Lehner B (2013) Genotype to phenotype: lessons from model organisms for human genetics. *Nat Rev Genet* 14(3):168-178.

2. Burga A & Lehner B (2012) Beyond genotype to phenotype: why the phenotype of an individual cannot always be predicted from their genome sequence and the environment that they experience. *FEBS J* 279(20):3765-3773.

3. Burga A, *et al.* (2011) Predicting mutation outcome from early stochastic variation in genetic interaction partners. *Nature* 480(7376):250-253.

Of ropes, rings, wires and chromosomes

by
Prof Kim
Nasmyth

Scientists are not immune to the temptation of believing that successful discoveries are largely attributable to their talent and hard work. Though these qualities undoubtedly do contribute, they are usually given more credit than they deserve. The roles of luck and contingency are invariably underplayed. Geniuses and their masterpieces do not emerge like butterflies from their chrysalides, but are very much products of their time. Luck plays its part at two stages. Those who make the sorts of discoveries that make it into textbooks were lucky to be around at a time when the problem that they solved was ripe for the picking. They were also lucky to have had an upbringing, education and set of experiences that made them eligible for the gifts that chance would provide, all in addition to being beneficiaries of a set of genes that may have predisposed them to being discoverers.

The quest for any scientist seeking a small patch of intellectual immortality is either to observe a new phenomenon, to describe a new problem, or to articulate its solution, above all else before anyone else does so. There are no prizes of any shape or size for coming second, even if this can be attributed to back luck. There are many cases in which being first is merely a matter of bringing greater force to bear on a problem that has already been well defined, which usually boils down to having more money. Those who are in possession of greater resources, needless to say, spend much of their time trying to persuade the world that their problems are important and difficult ones. This seems to work in the short term but rarely in the long run. With the benefit of hindsight, it is all too apparent that no great insight altering the course of our thinking has emerged. Most fields of science are littered with 'emperors who have no clothes'. For ordinary mortals with limited resources, it is therefore advisable to avoid the well trodden paths on which those with greater resources are likely to prevail. This means concentrating on the fruit that is thought by most to be out of reach, focusing on problems whose importance is underappreciated, or best of all being the first to realise that there is in fact a problem.

An important ingredient for success is to approach problems from a unique perspective. How to generate this individuality and to bring it to bear is probably harder today than it has ever been. With a world inter-connected by the Internet and a conference circuit so bloated that it keeps airlines afloat, it is ever harder for researchers to create and maintain unique intellectual profiles. Though geographical isolation in the past had its disadvantages, it did at least foster intellectual heterogeneity, a feature crucial for 'fresh' thinking. It is no co-incidence that Mendel working in the Moravian boonies broke open the heredity problem and not Darwin, who was surrounded and defended by fellows of the Royal Society. The parallels with biological speciation are too obvious and, in Darwin's failure, ironic.

How then best to create and maintain a small bubble of intellectual individuality within this sea of homogeneity? If luck and contingency are important for making discoveries, then fostering such uniqueness is one of the ways we can manage our luck. You cannot win the lottery jackpot if many others also possess a winning number! There is no formula but three things spring to mind. One is to read avidly and in a manner not necessarily driven by your research area. Idiosyncrasies in one's choice of reading matter help create unique points of view. Another is to spend more time talking to your immediate colleagues, especially those who do not work in your field. Your colleagues will be unique to you and if discussions with them provide insight, then it is less likely to be available to others. A third is to cultivate interests beyond your own work that might in unpredictable ways influence what you think or how you approach your work.

The latter can be more fun than the former. Moreover, doing things that are very different has the added advantage that it tends to clear the mind, enabling one to return to work with a greater perspective. Pre-occupations fade from view when mind and body are otherwise occupied and fortunately often do not re-emerge after a break. I have had two main outside interests or hobbies during the course of my research career. The first was climbing and mountaineering,

mainly in Austria where I worked for nearly 20 years. More recently, as both my nerves and limbs started to wear out, I have turned to running a small vineyard in the south of France. Both activities relieved the pressures of work and have provided a plan B for when research was in the doldrums. More important still, they actually provided brief flashes of insight into my research.

Rope management is an important aspect of climbing. Wasting time disentangling ropes that have knotted slows you down, which can prevent you getting off the climb before night descends or before bad weather arrives. Knots can also be potentially lethal when they form spontaneously at the end of a rope being retrieved from higher up the mountain during an abseil. When climbing with two ropes, advisable if retreat by abseiling proves necessary, it is crucial that the leader consistently clips one of these into carabiners attached to rock or ice on the left while the other is clipped into carabiners on the right. Meanwhile, their partner, who is paying out both ropes, must ensure that both pass seamlessly through their belaying device without causing tangles between the two 'downstream' ropes piled at their feet. Such tangles arise quite frequently because belaying devices impart twist and eventually supercoiling to ropes, which greatly increases the probability of tangling. Here then are many of the features of DNA as it emerges from replication forks. Unlike cells, climbers do not have anything analogous to topo-isomerases, which greatly facilitate disentanglement. Cutting a rope is an act of desperation, a method of last resort. Ropes must instead be managed by keeping stretches of rope separate from other ropes or from distant stretches of the same one.

Many years later, these lessons were brought home to me in a very different context, namely in the vineyard, where the wires from trellising systems have a tendency to entangle (Figure 1), again because they are inherently twisted having been laid from long coils and therefore have a tendency to supercoil. Left must be kept from right and upper from lower etc. With their greater stiffness, the wires used in trellising systems are, if anything, an even better analogy for DNA than climbing ropes. Climbing ropes on the other hand are designed to be highly elastic – not a property of DNA itself but one of DNA packaged into nucleosomes. Elasticity is a feature of chromatin whose importance has probably been hitherto under-appreciated. It is certainly an important aspect of chromatin in the vicinity of kinetochores where DNA strands are pulled around by microtubules.

The latter part of my research career has been spent studying the mechanism by which chromatin fibres are held together within chromosomes. This takes place not only along the longitudinal axes of chromatids (an important aspect of chromosome condensation) but also between sister chromatids (known as sister chromatid cohesion). Condensation and cohesion are mediated by a pair of related multi-subunit complexes called condensin and cohesin, respectively. When we discovered that cohesin's Smc1, Smc3, and kleisin subunits formed a tripartite ring structure and that sister chromatid

Figure 1: Trellising wires share many properties with supercoiled DNA – so why doesn't our DNA end up looking like this?

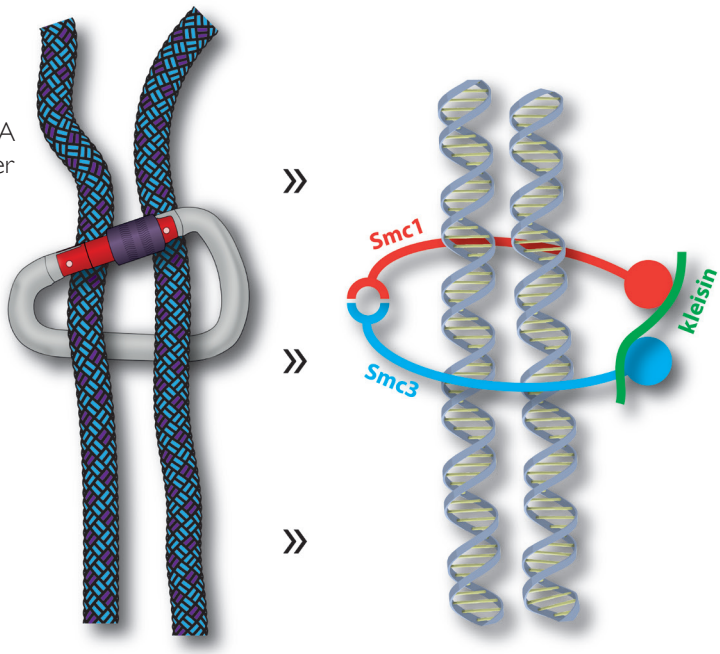

Figure 2: The trimeric cohesion complex may hold sister DNA strands together by entrapping them like a carabiner used in climbing.

disjunction is triggered by cleavage of cohesin's kleisin subunit by a protease called separase, it seemed perfectly natural to suppose that cohesin acted like a carabiner, holding DNAs together by entrapping them (Figure 2). Interestingly, another group published EM pictures consistent with the notion that cohesin formed a ring structure but did not point out this feature, let alone appreciate its potential significance. I do not think that they were particularly unimaginative. Instead, I had been lucky that my experience with climbing ropes had helped me to think topologically. I remain convinced, albeit in the absence of much evidence, that condensin must function using the same fundamental principle. In other words, like ropes and wires, chromosomes are tied not glued together.

The climbing rope analogy has continued to dominate my thinking about cohesin and its cousin condensin ever since. If cohesin ties DNAs together by entrapping them within its proteinaceous ring, then, like a carabiner, it must have gates through which DNA strands must pass. Identifying cohesin's DNA entry and exit gates and elucidating their mode of action has therefore been a high priority, and the fate of the ring model largely depends on the outcome of this line of research. I suspect that the enzymology of these gates will prove to be a fascinating and important area of chromosome research. Though still incomplete in many important details, the ring model has provided a fruitful intellectual framework for thinking about Smc/kleisin complexes, which are amongst the most conserved of all enzymes concerned with the chemistry and physics of DNA. My experience with wires and ropes tells me that even if I am wrong about Smc/kleisin complexes being topological devices, then something else must fulfil this function within chromosomes. In other words, the ring model is not one that should willingly be forsaken. Currently, Smc/kleisin complexes like condensin and cohesin appear to be the only realistic candidates for activities that simply must exist in organisms with large DNA genomes.

I think that climbing has influenced my scientific career in yet another important way. Getting it wrong at the sharp end of a rope in the mountains can have deadly consequences, which is rarely the case in most other sports undertaken as hobbies. Though everyone recognises that climbing is deadly serious, it is not always equally clear that the same is true for science. Most literature about scientific careers stresses the fun of doing experiments and the joys of discovery but it rarely emphasises that working out how the world works is a difficult and serious business. There is absolutely no point merely turning up at the office. If getting at the truth is a serious business, so is deciding whether the problem you are studying is an important one. It is all too easy to find problems whose solution will lead nowhere or have no lasting impact on society.

One last abiding feature that science and climbing have in common is that in their purest form, they are battles not with other human beings but with nature. Competition with other people can intervene in both activities, but most climbers will tell you that this is rarely an overriding aspect and never the reason why they climb. It is the challenge of pitting one's wits and body against a natural obstacle as well as the clarity of one's goal. This is equally the case in science. The competition is not really with other scientists. It is with the natural world that rarely reveals its secrets willingly. Of course, others will sooner or later take up the challenge and whether you or they get the answer first will depend on who was lucky to be the right person at the right place and time and above all else did not 'drop the ball' when it was passed. Thus science is a virtuoso activity more analogous to playing in a string quartet than in an orchestra. Like all virtuoso activities, the thrill of being continually on the edge of an intellectual or physical precipice and yet maintaining one's balance can be enormously rewarding and fulfilling.

Prof Kim Nasmyth FRS holds the Whitley Chair of Biochemistry and was Head of Department from 2006 to 2011.

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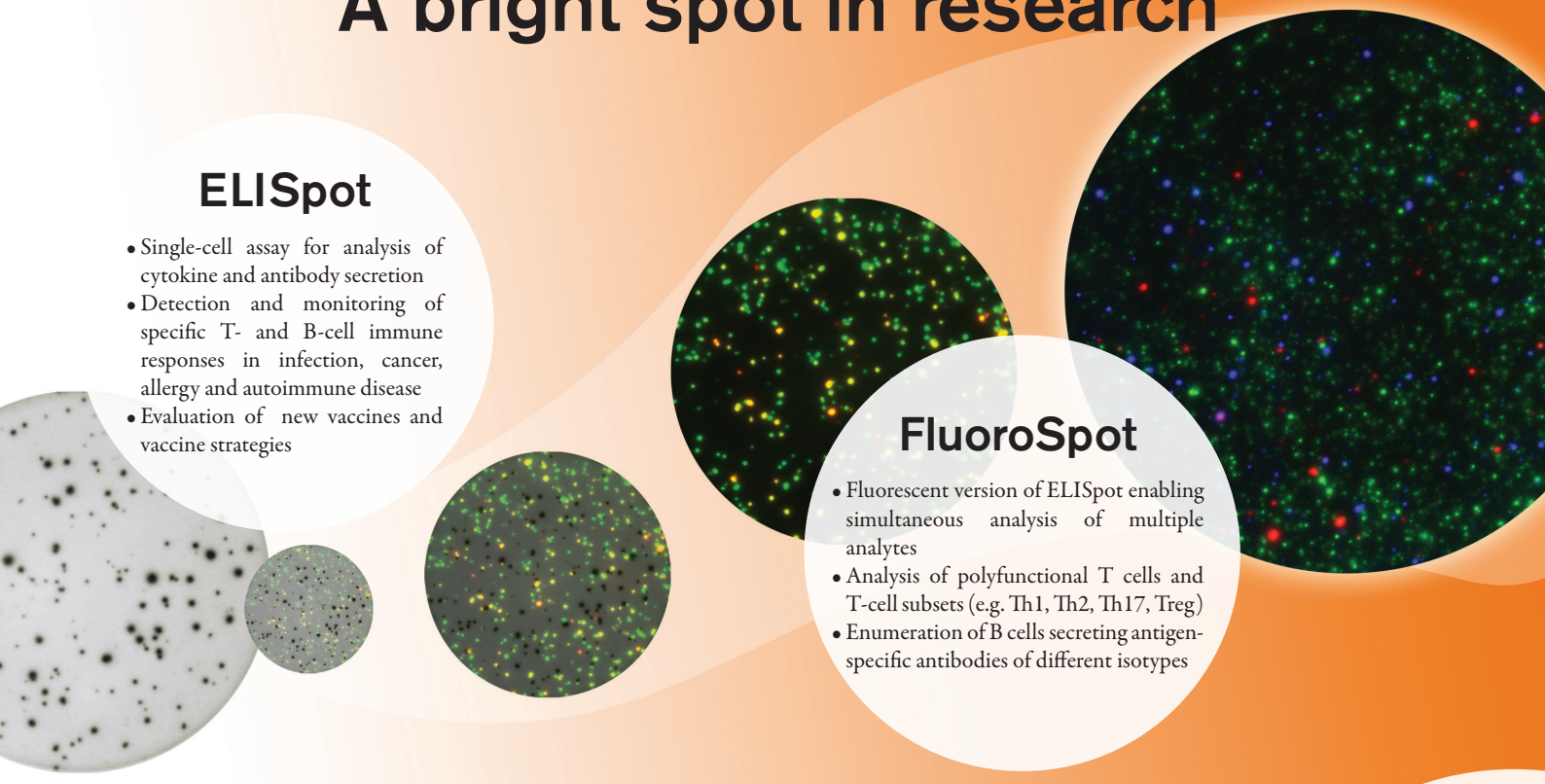

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From fiction to fact: Jurassic Park comes to life?

by Rupal Mistry

Picture taking your children to the zoo and seeing a Tasmanian tiger proudly prancing in its cage, as if it never left us. Or imagine the skies heavy with pigeons – not just any pigeons: passenger pigeons. Passenger pigeons took their last flight early in the 20th century and the Tasmanian tiger vanished in the 1930s. These and other extinct species may soon occupy more than textbooks, as scientists are pursuing what once seemed impossible: de-extinction.

The idea of de-extinction has fascinated scientists in the genomic era not only since Michael Crichton unleashed the dinosaurs of Jurassic Park in 1990. Thirteen years later, French and Spanish scientists successfully cloned the last known Pyrenean ibex from a frozen tissue sample. Celia was one of a species of superior-looking wild goat that disappeared in 2000 after excessive hunting in the 19th and early 20th centuries. Following Celia's death, José Folch led a team of reproductive physiologists to create her clone. A process called 'somatic cell nuclear transfer', previously used to produce Dolly the sheep, was implemented: goat egg cells were emptied of their own DNA and replaced with Celia's nuclei. The scientists then implanted 57 transgenic eggs into surrogate mothers. Seven pregnancies resulted, though six ended in miscarriage. The seventh surrogate carried Celia's clone to term. However, an extra lobe was discovered on one of her lungs at birth. The kid withstood only seven minutes of life (1).

The event was groundbreaking. Although her life was short, Celia's clone proved that de-extinction was possible. The excitement from such advances has led geneticists, conservationists, wildlife biologists and others to come together for the first time to discuss de-extinction: could, and, more importantly, should it be done?

The notion of de-extinction provokes debate about which organisms we want back. Among the top candidates are the passenger pigeon, Tasmanian tiger, woolly mammoth, gastric brooding frog and sabre-toothed cat. The idea of bringing back vanished species has encouraged scientists to examine the quality of DNA from museum specimens and more recent samples, leading to the piecing together of the genomes of extinct species.

Tissue from the enormous woolly mammoth that walked the earth during the last ice age was found in the frozen cliffs along the Yana River in Yakutsk, Siberia. Amongst the preserved bone marrow, hair, skin and fat, scientists in Seoul are hoping to find an entire cell. In the unlikely event that they do, they plan to clone a woolly mammoth by making induced pluripotent stem cells, a novel cloning technology superior to the somatic cell nuclear transfer used in the creation of Dolly. This technology allows differentiated cells to be reverted back to an embryonic stem cell-like state by being driven to express the necessary genes to maintain this state. These cells can then be re-differentiated into germ cells, and further influenced to become embryos. With the ability to reverse differentiation, de-extinction is surely within our grasp. A single mammoth cell could be manipulated to become millions of cells that could be further reprogrammed

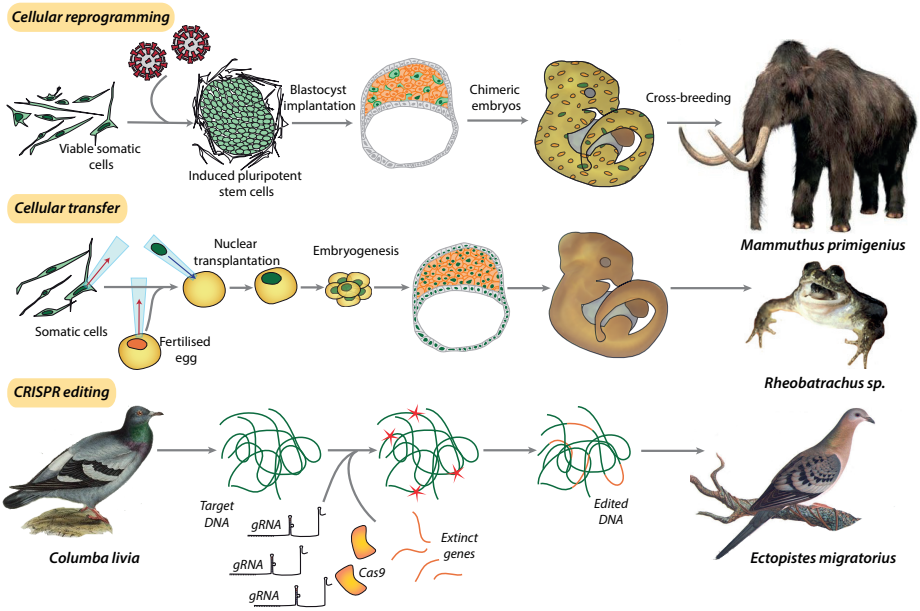


Figure 1: Three methods discussed for de-extinction. Figure by Óscar Cordero Llana.

to grow into embryos ready for implantation into surrogate elephants. The chances of finding a viable cell, however, are very slim. Instead, creating a whole organism from a single intact nucleus, while significantly more difficult, could still be possible. If an elephant egg cell could be harvested – a task that has yet to be achieved – the nucleus could be replaced with one from a mammoth and an electric shock would induce cell division. The transgenic egg would continue to divide into a mammoth embryo, which could then be transplanted into a surrogate elephant. If all were to go well, two years later, a baby mammoth would be born.

As complicated as it is to clone a mammoth from just an intact nucleus, bringing back the red-breasted passenger pigeon, *Ectopistes migratorius*, is no easier. Bird embryos develop inside shells, precluding the usual cloning techniques, and the lack of a preserved functional genome further hampers efforts. George Church, professor of genetics at Harvard University, has developed a new genome editing method that may overcome these challenges and bring back the passenger pigeon, or any extinct species for that matter. CRISPRs (clustered regularly interspaced short palindromic repeats) were discovered as part of a gene silencing mechanism of resistance against foreign DNA in bacteria and archaea. Cas proteins and guide RNAs cleave genomic DNA at CRISPR sites to form an entry site in the bacterial genome, allowing cleaved endogenous DNA to be incorporated (Figure 1). As a result, this DNA when transcribed can recognise, and thereafter silence, foreign DNA. Church has exploited the site-specific DNA-cutting ability of this system as a potent means of targeted genome editing in any organism (2). Theoretically, this mechanism allows one to take genes for particular traits – such as the gene for the passenger pigeon's long tail – and splice them into the genome of a stem cell from a genetically similar animal still in existence, such as a rock pigeon. Resulting transgenic stem cells could then be induced to become egg and sperm precursor cells and be injected into fertilised rock pigeon eggs, where they would drift to the sex organs of the developing embryos. The newly hatched squabs would appear like normal rock pigeons, yet their eggs and sperm would be transgenic. After maturing and mating, the next generation of squabs would have the desired passenger pigeon traits. Over time, scientists could select birds with passenger pigeon traits and eventually create the final product.

Some species became extinct just as they were being understood. One such species is the gastric brooding frog found in Queensland, Australia, which vanished in the 1980s. Scientists are eager to reinstate this particular amphibian due to its extraordinary method of reproduction. The female would lay thousands of eggs, thereafter fertilised by the male. Then, astonishingly, the female would swallow the eggs, converting her stomach into a cosy womb. A few weeks later, she would give birth to her brood through her mouth. The embryos were protected from the fatal stomach acid by a surrounding jelly containing prostaglandins, turning off the production of hydrochloric acid. Scientists plan to replace nuclei from the Australian marsh frog and barred frog with nuclei from the gastric brooding frog in a similar process to that for Celia. Despite the difficulties of working with frog eggs – they start to lose potency after a couple of hours and cannot be frozen – scientists have already successfully created embryos (3).

In the long run, the current difficulties are merely bumps in the road and true de-extinction is within reaching distance. Researchers will soon face other challenges, such as the ethical issues around releasing these genetically engineered organisms into the wild. The possibility exists that if the re-created organisms were unleashed, they could become a pool for a lethal virus. Even if they are perfectly safe to other organisms, where will they go? Many of the places that these species called home no longer exist. On the other hand, some will argue that we have a duty to make de-extinction work, as we are responsible for the disappearance of many species after destroying their habitats and hunting them for their fur, horns or simply for sport. Conservationists argue that we must first deal with currently threatened species. The Amur leopard, the black rhino, the cross-river gorilla and the hawksbill turtle are only a handful of critically endangered species of which we already struggle to maintain stable populations.

The possibility of de-extinction appears increasingly likely by the day, but reveals ethical implications and consequences. We may never have to fear the loss of any species again. With cutting-edge cloning research plus viable DNA and a bit of luck, we could be walking the earth with species to which we thought we had said our final goodbye.

References

1. Gannon M (2013) Reviving the Woolly Mammoth: Will De-Extinction Become Reality? *Live Science*. Available at http://www.livescience.com/27939-reviving-extinct-animals-mammoths.html [Accessed June 2013].

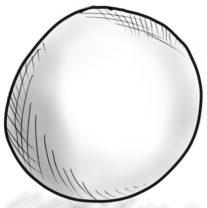
2. de Souza N (2013) CRISPR silencing. *Nat Methods* 10(5): 380–381.

3. Zimmer C (2013) Bringing them back to life. *National Geographic*. Available at http://ngm.nationalgeographic.com/2013/04/125-species-revival/zimmer-text [Accessed June 2013].

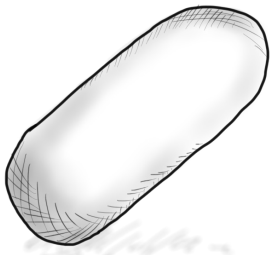
Rupal Mistry is a 2nd year DPhil student working in the Ligoxygakis group in Biochemistry.

The Shape of a Cell

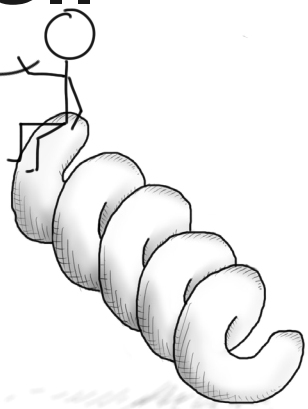
What shape is a bacterial cell?
These three are probably the most famous examples...



Spheres (cocci)
e.g. *Streptococci*



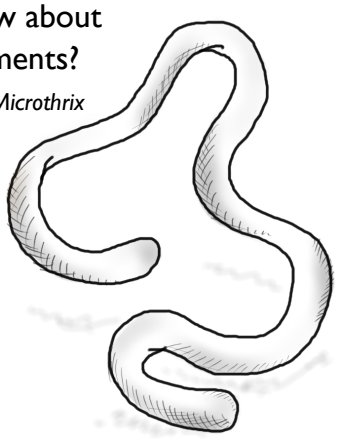
Rods (bacilli)
e.g. *Escherichia*



Spirals (spirochetes)
e.g. *Borrelia*

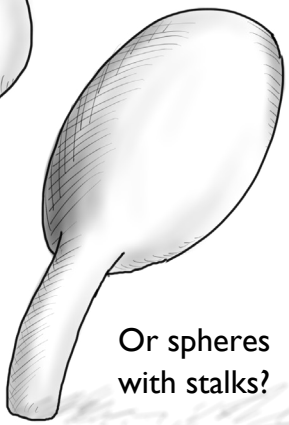
...but this barely scratches the surface! The actual diversity of bacterial shape is *enormous*.

How about filaments?
e.g. *Microthrix*

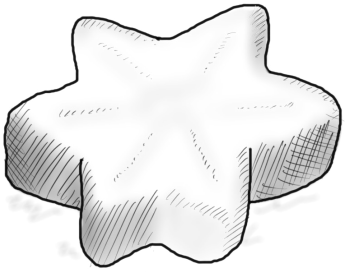


Or spiraly filaments?
e.g. *Leptospira*

More spherical spirals?
e.g. *Helicobacter*



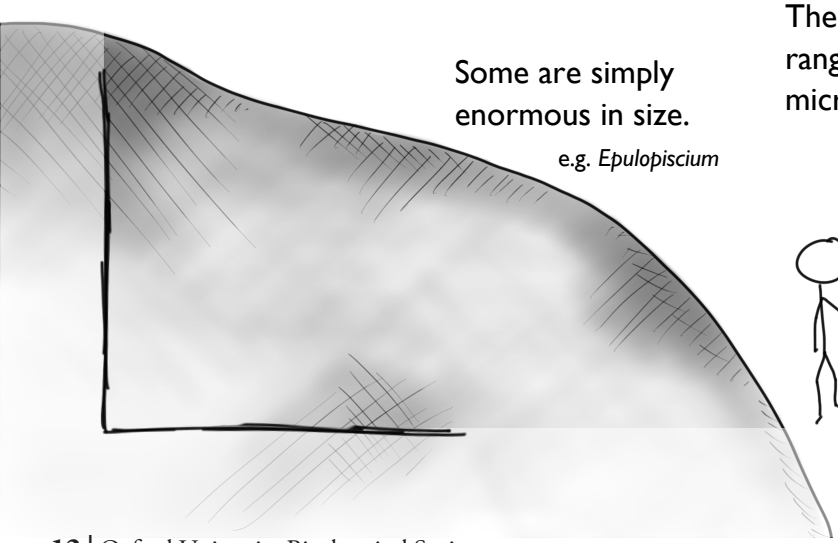
Or spheres with stalks?
e.g. *Caulobacter*



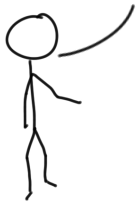
How about star shaped plates?
e.g. *Stella*

Even this is still a tiny selection. Within each of these classes there is massive variation; branched or unbranched filaments, spirals of different widths and pitches, different degrees of sphericity, shapes of plates, numbers of stalks, etc.

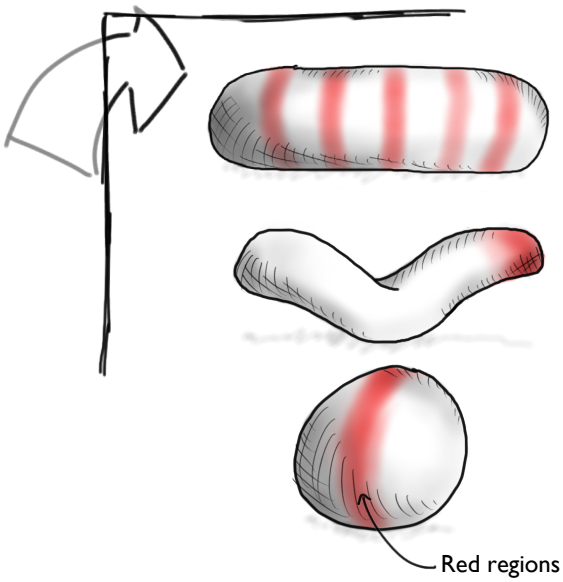
There is also a huge range of bacteria sizes, ranging from around 0.2 to well over 200 microns.



Some are simply enormous in size.
e.g. *Epulopiscium*



There are two huge open questions:
How do bacteria attain this huge diversity of cell shape?
Why do they? What is the functional role of shape?



Zonal growth
e.g. Escherichia

Polar growth
e.g. Streptomyces

Septal growth
e.g. Staphylococcus

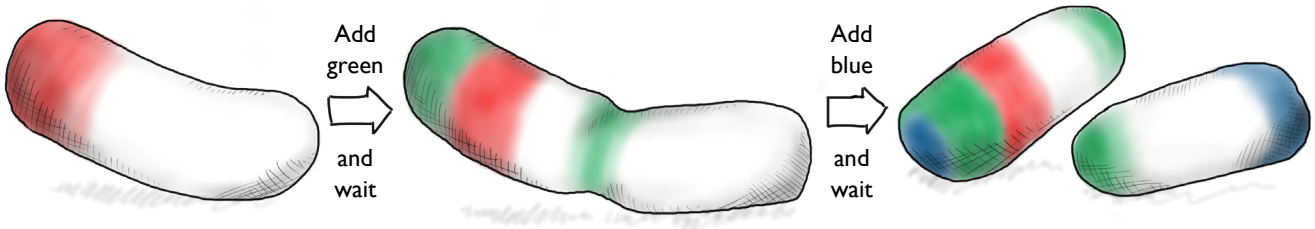
Red regions map where the new cell wall is built

How is the easier question to answer:

The bacterial cell wall is made of peptidoglyan and is built using the unusual D-isomers of some amino acids.

If you add red fluorescent D-amino acids to bacteria they build it into growing parts of the cell wall. This maps exactly where the cell grows, and different patterns of growth can explain how different bacterial shapes are made.

Even better, if you add several different colour fluorescent D-amino acids in succession they map where the cell grows over time, including when it divides...

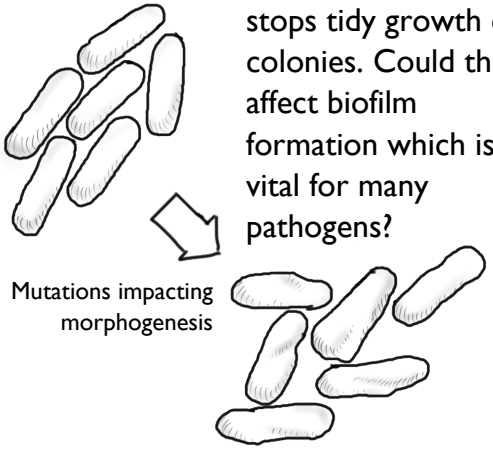


Why is definitely a more challenging question!

In fact, the function of cell shape in most cells is not well understood. This is a crazy gap in our knowledge; it's the cellular equivalent of not knowing legs are handy on the land, and flippers and fins are great underwater! So what might shape do?

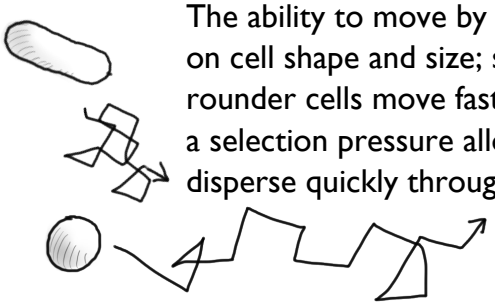
Growing in a community?

e.g. Escherichia



Disrupted cell shape stops tidy growth of colonies. Could this affect biofilm formation which is vital for many pathogens?

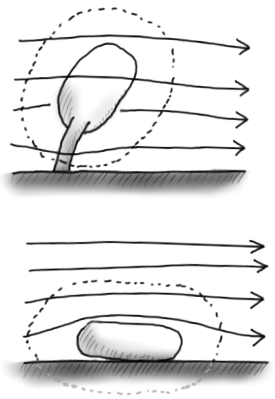
Moving by diffusion?



The ability to move by diffusion depends on cell shape and size; smaller and rounder cells move faster. Could this be a selection pressure allowing bacteria to disperse quickly through liquids?

Gathering nutrients?

e.g. Caulobacter



Cells with stalks look like they are better at grabbing nutrients when attached to a surface in a fluid flow. Is that the function of the stalks?

So what about the spirals? And the stars?
Or the filaments? Are they for nutrient access?
Surface attachment? Communal growth? Swimming?
Flotation? Avoiding predation?
There are still a lot **of questions!**

By Richard Wheeler 2013

Kuru et al. (2012) Angew. Chem. Int. Ed. Engl.
Young (2006) Microbiol. Mol. Biol. Rev.

Measuring research impact on the web

by
Iain
Hrynaszkiewicz

How research impact is measured is very important to researchers, their institutions and their funding agencies. Impact helps determine who gets hired, who gets promoted and who gets funding. Ironically, the measurement of scientific impact and quality is often very unscientific. But by making use of new 'alternative' metrics, driven by web-based technology, we are able to gain a better understanding of the diverse impacts of research.

Most life science researchers will have heard of the Journal Impact Factor. However, there is growing realisation that the Impact Factor, while sometimes useful for assessing the quality of entire journals (1), is not appropriate for assessing the quality and impact of individual papers or individual researchers (2).

The Impact Factor is an average of the number of citations per citable paper published in the previous two years for the entire journal (Figure 1), and is therefore irrelevant when assessing a paper published more recently. As an average value it is also easily skewed by outliers (see Table 1 for an evaluation of the Impact Factor as a research and bibliographic metric).

$$\text{IMPACT FACTOR} = \frac{\text{Citations in [year] of articles published in [previous 2 years]}}{\text{Number of 'citable' articles published in [previous 2 years]}}$$

Figure 1: The Impact Factor calculation.

Advantages
Calculations are reproducible
Curated – human filtering and correction
Can help predict journal quality
Transparent calculation (to some extent)

Disadvantages
Slow – delay of up to 2 years
Data not publicly available
Poor predictor of paper and researcher quality
Can be manipulated by authors and editors

Table 1: Advantages and disadvantages of Impact Factors as a metric.

The flawed practice of using Impact Factors to judge individual papers and grant applications is slowly changing. In May 2013 the San Francisco Declaration on Research Assessment (DORA, 3) was launched, with supporting editorials in *Science*, *Journal of Cell Biology* and other publications. The aim of DORA is to use more appropriate – and more scientific – ways to judge the impact of individual research projects, and by June 2013 the declaration had attracted around 9,000 signatures, including entire organisations such as Faculty of 1000. Importantly, funders are beginning to change their policies on how impact is assessed. Research Councils UK, which fund £3 billion of research per year, announced in April 2013 that the Impact Factor of a journal where an author intends to publish is no longer important (4).

In recent years, more and more scientific research has been carried out and shared online through a variety of websites and databases. This has created a diverse collection of digital research 'products' going beyond papers in journals, and the usage and citations of these products need to be, and are being, measured (5). For example, software from bioinformatics projects are published in the source code repository Github; life science datasets are published in repositories such as Dryad, figshare and in NCBI databases; conference posters are deposited in F1000Posters and slides are often shared in Slideshare. With the growing use of social media such as Twitter, academic bookmarking and reference management services such as Mendeley, and post-publication peer-review services such as F1000Prime, there are many ways in which we now interact with research products in their various repositories. All of these interactions – the number of tweets, bookmarks, citations on science blogs, F1000Prime scores – can be measured and aggregated to gain understanding of the importance of science beyond traditional citations. These non-citation metrics are known collectively as alternative metrics ('altmetrics') and are being increasingly used.

Citations of individual papers and specific collections of papers remain important. There are several, often free, web-based tools for measuring citations. Google Scholar and Microsoft Academic Search both provide services that enable a researcher to collect papers and determine personal citation share and Hirsch-index (h-index) – an indication of how many highly cited papers an individual has published.

Using altmetrics in addition to citation metrics is advantageous as it provides more information from more sources, which in turn means we can understand more about the impact of research. But like citation metrics, altmetrics have some limitations (Table 2).

With many types of metrics now available, web-based tools have emerged that aggregate metrics from different sources and provide an aggregate scoring and assessment of articles or collections. One such tool is from the company Altmetric, which provides services primarily to publishers interested in altmetrics and measures the 'buzz' around published papers. Scores provided by Altmetric include the number of tweets, Facebook 'likes', F1000Prime score and other data sources (6). ImpactStory is a free service that individuals can use to create customised impact reports. As well as published papers, ImpactStory can be used to measure the usage of datasets, software, slides and science blogs (7). ImpactStory measures social media interactions as well as citations of all digital research products, and applies tags to denote different levels of usage and interaction. These tags include 'cited' or 'highly cited', 'discussed' or 'highly discussed' (on social media), 'viewed' or 'highly viewed' (downloaded) and 'recommended' (in F1000Prime). Other altmetrics tools include ScienceCard, Plum Analytics and ReaderMeter.

Advantages
Fast – data can be available immediately
Lots of openly available data and tools emerging
Impact of all research products can be tracked
Broader picture of impact than citations

Disadvantages
Heterogeneity in results, depending on tool used
Some tools may not be around for the long term
Can be manipulated or 'gamed'
Results not always reproducible (evanescent)

Table 2: Advantages and disadvantages of altmetrics.

Tools to generate altmetrics aggregate large amounts of numerical, machine-readable data and interpret these data programmatically through comparisons to similar articles. However, our understanding of altmetric data and impact more generally is improved with human-readable information (context) about why a particular paper is important. For example, the F1000Prime article recommendation service aims to provide data with context – a numerical score, along with a written comment of recommendation by the scientist who selected the article. A 'faculty' of about 5,000 peer-nominated scientists assisted by a similar number of associates contribute to F1000Prime. They select and rate important articles in biology and medicine – about 2-3% of the literature – helping scientists find what they need to read in the ever-growing body of literature.

Increasing use of altmetrics by funders and initiatives such as DORA are positive developments for research assessment, helping to move far beyond the Impact Factor. It is important, however, to recognise that some of the most important types of impact are not easily measurable with either the alternative metrics or the citation metrics so far described. Changes to clinical practice or influence of policy decisions, considered by the Medical Research Council (8), are good examples. Even altmetrics with their finger on the pulse of social media may not easily measure the societal or scientific importance of some studies. Consider a randomised controlled trial, which finds that a widely available antibiotic can halve the number of deaths in children with HIV-1 (9). Regardless of citations, downloads, tweets or recommendations of this paper, it unequivocally has impact (10).

Figure 2: Image by Don Davis/ NASA (public domain).

Notice of co-publication: Substantial parts of this article will be translated and re-published in a Russian language journal, *University Book*, later in 2013.

References

1. Saha S, *et al.* (2003) Impact factor: a valid measure of journal quality? *J Med Libr Assoc* 91(1): 42–46.

2. Seglen PO (1997) Why the impact factor of jounals should not be used for evaluating research. *BMJ* 314(7079):498–502.

3. San Francisco Declaration on Research Assessment (2012). Available at http://am.ascb.org/dora/files/SFDeclarationFINAL.pdf [Accessed June 2013].

4. RCUK Policy on Open Access and Supporting Guidance (2013). Available at http://www.rcuk.ac.uk/documents/documents/RCUKOpenAccessPolicy.pdf [Accessed June 2013].

5. Piwowar H (2013) Altmetrics: Value all research products. *Nature* 493(7431):159.

6. See http://www.altmetric.com/details.php?citation_id=938211 for an article with an Altmetric score.

7. See http://impactstory.org/collection/v7b25c for an example collection of the author's work.

8. Viney I (2013) Altmetrics: Research council responds. *Nature* 494(7436):176.

9. Chintu C, *et al.* (2004) Co-trimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): a double-blind randomised placebo-controlled trial. *Lancet* 364(9448):1865–1871.

10. Hrynaszkiewicz I (2013) What is impact? Available at http://blog.f1000.com/2013/05/20/what-is-impact/ [Accessed May 2013].

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Looking back on autism research

by Hannah Buxton

70 years ago, Leo Kanner published a seminal paper describing 11 case studies of children that he believed shared a common autistic syndrome of disturbances of affective contact (1). Since then, scientists have searched for the cause of autism. The answer still eludes us. Looking back, what road has autism research taken, and where can we hope it will lead in the future?

Kanner's original observations shaped our definition of autism, and his paper still resonates in the diagnostic criteria used today. There is, as yet, no biomarker for autism, and so the condition is diagnosed on the basis of behavioural symptoms. Back in 1943, Kanner noted that the children were unable to relate to others, showing "extreme autistic aloneness" and monotonous, repetitive behaviour with an "insistence on sameness". Today, the Diagnostics and Statistical Manual IV used to diagnose autism defines symptoms in three categories, known as the autism triad: impaired communication, poor social reciprocity, and restricted interests.

Kanner also noticed that the children all came from educated, professional backgrounds and that in his sample there were "very few really warm-hearted fathers and mothers". These passing comments foreshadowed the rise of the dominant theory of autism from the 50s to the 70s: that autism was the fault of the parents. This damaging theory was championed by Bruno Bettelheim. He argued that parents of children with autism were themselves psychologically abnormal, and unable to react to their babies like normal parents. Mothers of autistic children were said to meet their child's physical needs (e.g. food), but in a mechanical way, without affection. Thus, this theory became known as the 'refrigerator mother' theory. In reaction to their parents' emotional neglect, the children withdrew. This was autism.

For decades, mothers were told they had permanently damaged their children by consciously or unconsciously rejecting them despite a lack of solid evidence that the parents of autistic children differed in any way from parents of non-autistic children. Bettelheim went so far as to compare the environment created by 'refrigerator mothers' to his experience in a Nazi concentration camp. Bettelheim's shadow still permeates the field, and in some countries his book *The Empty Fortress* is still the go-to book on autism.

After the horrors of the eugenics movement in Nazi Germany during WW2 the world was (perhaps understandably) reluctant to accept a biological cause for autism, or any other disability for that matter. Thus, the 'refrigerator mother' theory remained firmly in place during a time when psychoanalysis was hugely popular. Nonetheless, this view was not accepted by all. Bernard Rimland, an experimental psychologist with an autistic son, highlighted that many autistic children have parents who do not fit the cold 'autistic parent' personality type, and that parents who fit this type often have non-autistic children. He also noted the high concordance rate of autism in identical twins, the high sex ratio, and that children with autism appear abnormal soon after birth, before being exposed to the supposedly damaging familial environment. All this, Rimland argued, seemed to suggest a biological cause of autism (2).

In 1977, Folstein and Rutter published a twin study providing strong evidence for a genetic basis for autism. They found that the rate of concordance was significantly higher for monozygotic (identical) twins than dizygotic (non-identical) twins (3). Some researchers have now even heralded autism as the most hereditary of all the psychopathologies.

The field of autism finally dragged itself out of the psychoanalytic era and into the age of genetics and cognitive science. Various theories for autism have been proposed in the last three decades including that autism is case of an "extreme male brain", dominated by a systemising approach to the world (4). Others have posited that autism is caused by problems with imitation, an infant skill that is crucial for normal social and communicative development (5). Two highly influential explanations include the theory of mind (TOM) account, and the weak central coherence (WCC) account.

The TOM account describes our ability to understand others' mental states, beliefs and desires, and to appreciate that they are different to our own. Experiments using various TOM tasks suggest that individuals with autism have difficulty representing the mental states of others. Those autistic individuals who do achieve TOM, do so by an alternative route. A deficit in TOM could underlie social and communication problems experienced by individuals with autism.

Of course, the TOM account only addresses the social deficits in autism. What about the other symptoms of autism? How can we explain the cognitive and perceptual strengths? The WCC account, developed by Uta Frith and Francesca

Happé, offers some explanation of these: individuals process items in their environment as wholes, autistic individuals focus on local features, the details of objects (6).

Autistic individuals' superior performances on task such as the 'Embedded Figures Test' support the WCC account. Participants are shown a series of forms (such as a pram), and asked to find a smaller detail (such as a triangle) that is embedded in the bigger picture, as quickly as possible (Figure 1). To do this, you must ignore the bigger picture and focus on the elements that make up the object. Children with autism outperform typically developing children on this task, revealing a tendency to process information in a detail-based way (7). This processing style could also account for the extreme sensitivity autistic individuals show to changes in their environment.

The WCC account of autism is intriguing, but like the TOM account it is incomplete – this theory struggles to explain the social deficits of autism. Indeed, no theory for autism has yet been able to satisfactorily account for all facets of the condition, both the social deficits and the non-social cognitive abnormalities, nor for the wide variation seen in the autistic population. Similarly, the search for a genetic explanation for autism has not yielded a simple answer. The closer scientists look, the more complex the picture turns out to be.

Psychologists are now calling for the field to move away from the search for 'the' explanation of autism. Research headed up by Francesca Happé suggests that the autism triad may be separately heritable, and that the field should consider how multiple deficits in different cognitive domains may work together to cause autism (8). This is both an exciting and daunting step for the field. Researchers are sacrificing parsimony, and considering more complex models than ever before.

While research into autism continues, families coping with an autistic child must continue to wait for answers. Without a solid theory, the development of successful interventions has been slow. Currently a diagnosis does not really direct a child to any specific form of treatment. The question marks surrounding the aetiology of the disorder have left a dangerous hole for quacks, pseudo-science and scare campaigns. A dissection of all of the misguided alternative treatments and bad PR that the field of autism has endured over the years could fill a whole book, never mind the remainder of this article.

Looking back, there have been colossal changes in autism theories over the last 70 years. It was considered an extreme defence mechanism to deal with unconscious rejection of one's own family. Now it is considered a neurological disorder, with a large complex genetic component, that impacts on how individuals relate to others, and how they process the world around them. As research goes forward, the scientific community has to be ready to accept that there are no simple answers to autism.

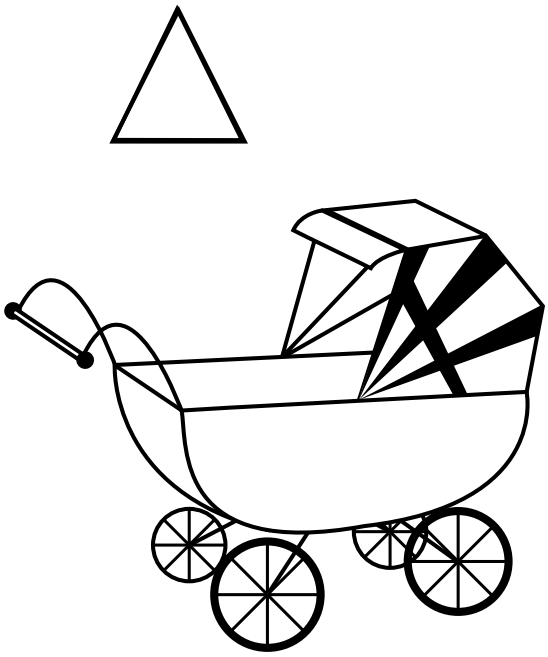

Figure 1: An item from the 'Embedded Figures Test'. Participants are instructed to find the target (the triangle) in the larger picture (the pram). Autistic individuals are significantly faster at this task.

References

1. Kanner L (1943) Autistic disturbances of affective contact. *Nerv Child* 2:217–250.

2. Rimland B (1964) Infantile autism: the syndrome and its implications for a neural theory of behaviour. New York: Appleton-Century-Crofts.

3. Folstein S & Rutter M (1977) Infantile autism: a genetic study of 21 twin pairs. *J Child Psychol Psychiatry* 18(4):297–321.

4. Baron-Cohen S (2002) The extreme male brain theory of autism. *Trends Cogn Sci* 6(6):248–254.

5. Rogers SJ & Pennington BF (1991) A theoretical approach to deficits in infantile autism. *Dev Psychopathol* 3(02):137-162.

6. Frith U & Happé F (1994) Autism: beyond "theory of mind". *Cognition* 50(1):115–132.

7. Shah A & Frith U (1983) An islet of ability in autistic children: a research note. *J Child Psychol Psychiatry* 24(4):613–620.

8. Happé F, *et al.* (2006) Time to give up on a single explanation for autism. *Nat Neurosci* 9(10):1218–1220.

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Chromatography to coins: Puridify's journey of commercialising nanofibre adsorbents for bioseparation

by Jenny Dworzak

Disruptive technology, dynamic teamwork, defined trajectory – those are the headings one would find in Puridify's playbook, a schema that won the world's largest biotech idea competition in May this year. In an estimated £200 billion industry and a world in which three out of four venture capital-backed startups fail, identifying determinants of success is invaluable. This is Puridify's roadmap to trumping their formidable competition at the 2013 Oxbridge Biotech Roundtable (OBR)-SROne-powered OneStart competition.

This article is co-featured on OBR's Review www.obrreview.com, a running conversation about science, business, and everything in between.

Disruptive Technology

Puridify's patented FibroSelect technology, the product of five years of research and CEO Oliver Hardick's UCL-based PhD, boasts the hallmarks of a disruptive technology. It promises reduced cost, complexity and investment risk. Currently, downstream processing and purification of biotherapeutics contribute to 50% of manufacturing costs and rely on archaic technologies, unaltered for 15 years. FibroSelect is an electrospun nanofibre adsorbent, projected to reduce biotherapeutic manufacturing costs by 40-90%.

How does FibroSelect promise to reduce these costs? FibroSelect's base material is cellulose: cheap, readily available, biodegradable and biocompatible. The polymer is electrospun in the form of cellulose acetate to ensure solubility. Electrospinning involves passing the cellulose acetate-solvent solution through a microneedle. A voltage is applied to the resultant droplet, inducing electrostatic forces that overcome surface tension to form a Taylor cone, which elongates into a cylindrical jet due to the high molecular cohesion within the polymer-solvent solution (Figure 1). As elongation proceeds, a phenomenon known as electrical bending instability produces a whipping motion in the polymer stream that stretches the fibre to a nanometre scale. The spun polymer is deposited on a plate from which the solvent is evaporated, leaving a solidifying fibre. This fibre is then treated to form regenerated cellulose and subsequently coupled to diethylaminoethanol, a process commonly used to form anion exchange surfaces (1).

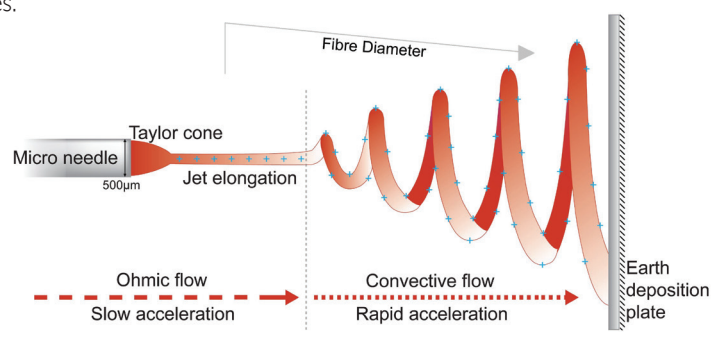

Figure 1: Electrospinning of nanofibres.

The current market standard for bioseparation is the use of packed beads, which has two major shortcomings. The first is pressure drop, or the increasing force required to maintain a constant flow of perfusate across the filter; when a system can no longer generate sufficient pressure to maintain flow, the separation column fails. The second drawback to this approach is limited flow rate due to the compressibility of the beads comprising the filter (2). An alternative to bead-based adsorbents is the porous membrane, which allows for higher flow rates. Porous membrane filtration capacity is, however, limited by pore size uniformity, axial and radial diffusion, and fouling, the increase in driving force required to maintain a set flux through the membrane. To avoid these undesirable effects, feed materials often require extensive pre-treatment (2).

Puridify's electrospun nanofibre adsorbent ensures a higher ratio of surface area to pore size, if polymer solvent properties are tightly controlled (1). The increased surface area and porosity allow for a maximal flow rate 100 times that of packed beads, with a ten-fold productivity increase and enhanced mass transfer capabilities (2).

FibroSelect was patented in 2011, after which Oliver received a 12-month Enterprise Fellowship from the Royal Society of Edinburgh to assess the commercial opportunity of the technology. Puridify was incorporated shortly afterwards in March 2013.

The OBR-SROne OneStart competition pitted Puridify against almost 100 other European-based biotech business ideas, 35 of which were selected to attend a semi-finalist boot camp event for business idea development in March 2013. Each semi-finalist received mentoring from industry professionals representing the likes of GlaxoSmithKline, Ernest&Young and Imperial Innovations. Ten selected finalists presented to a judging panel comprised of Jens Eckstein (SROne), Daniel Perez (OBR), Maria Bobadilla (Roche), Ian Tomlinson (GSK), Kate Bingham (SV Life Sciences) and Andrew Sandham (Kymab), who deemed Puridify the most promising candidate in the competition

(3). Why? Advice from the judging panel members themselves indicates that device innovation requires less time and resource to proof and develop and is more lucrative as a final product than drug development. While an average drug development to market timeline is 10-11 years, that for medical technology is only one to two years (4). FibroSelect could, according to Puridify, "revolutionise the entire cost structure and technological potential of the biotech industry". Furthermore, its ease of integration into the existent biotech infrastructure and its proof on a research scale contribute to the relatively low investment profile of this 'disruptive technology'.

Dynamic Team

In biotech entrepreneurship, a competitive product is necessary but is rarely sufficient to ensure success; content must be coupled with a cooperative and competent team. While Puridify's three-member team converged shortly after Oliver received his Royal Society of Edinburgh Enterprise Fellowship, the threesome had been friends for the preceding eight years. Tom acknowledges the team's closeness as a key strength, "[it makes] difficult decisions, such as our name [or] our logo, relatively easy". Oliver and Iwan (COO) both trained in engineering at UCL and have spent the past eight years in biotech-related academia or industry. As a former investment banker at Deutsche Bank and accountant at Deloitte, Tom provides finance and business expertise. Furthermore, their three-man executive team membership ensures there is always a majority when voting on important decisions.

Through OneStart's workshops and their own advisory board acquisition, this already strong team garnered important input from industry leaders and executive consultants resident at Stevenage Biocatalyst, CellCentric, Unicorn Biologics, University College London, GlaxoSmithKline, SROne, Merck Research Laboratories and London Business School. Puridify describes this OBR-enabled exposure to key industry professionals and investors as "invaluable".

Defined Trajectory

What does the future look like for Puridify? As winners of the OneStart competition, Puridify acquired £100,000 of prize money, Stevenage Bioscience Catalyst-hosted lab space, membership to life science networks, and access to business and intellectual property support. They aim to take FibroSelect to market in an estimated 36 months, where their imminent target is the manufacturing sector.

Puridify's future is not devoid of challenges. Convincing large-scale pharmaceutical companies to adopt a novel processing mechanism from a relatively small and young company will be a challenge. The team hopes to ease their entry into the biotech industry by limiting changes required for adoption of their technology and using pre-existent materials. Another major challenge will be scaling up in a timely manner.

As the OneStart boot camp and workshops indicated, another challenge intrinsic to device innovation as opposed to drug development in the biotech startup field is the specific management skillset demanded by the former, one that requires knowledge of working capital and inventory. When asked for their most valuable lessons from the OneStart experience, Puridify cites simplifying the pitching process. "As a startup, pitching is your gateway," they say, referencing valuable advice on the importance of a concise and directed gateway to garnering investors and business partners. Furthermore, relaxing their rigidity in business planning has proved beneficial as well. In these early stages of commercialising their bioseparation technology, Puridify say that "less is more". We'll watch their continued pursuit of that principle.

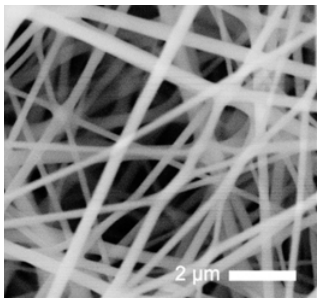

Figure 2: Scanning electron micrograph of Fibroselect at 2,500x magnification.

References

1. Hardick O, *et al.* (2012) Nanofiber adsorbents for high productivity downstream processing. *Biotechnol Bioeng* 110 (4):1119-1128.

2. Hardick O, *et al.* (2011) Nanofibre fabrication in a temperature and humidity controlled environment for improved fibre consistency. *J Mater Sci*, 46 (11):3890-3898.

3. Nandra K (2013) OneStart Winner Announced. Roundtable Review. Available at http://www.oxbridgebiotech.com/review/onestart/onestart-winner-announced/ [Accessed June 2013].

4. Nandra K (2013) OneStart Biotech Boot camp: Medical devices discussion panel. Roundtable Review. Available at http://www.oxbridgebiotech.com/review/onestart/onestart-biotech-bootcamp-medical-devices-discussion-panel/ [Accessed June 2013].

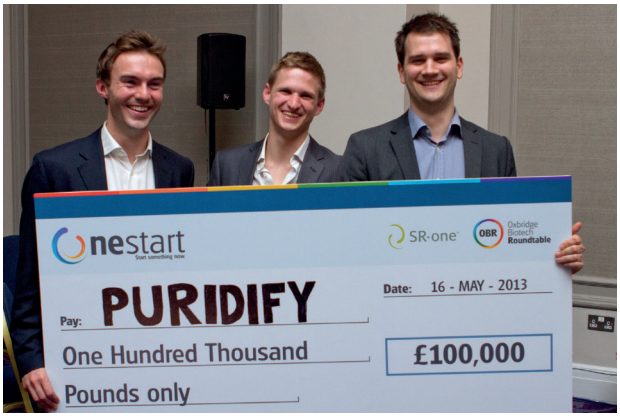

Figure 3: Puridify at the OneStart finals gala. From left to right: Tom Haywood (CFO), Oliver Hardick (CEO), and Iwan Roberts (COO) (from http://www.oxbridgebiotech.com/wp-content/uploads/2013/05/OBR-SRone-77.jpg).

Jenny Dworzak is an MD/PhD student at Icahn School of Medicine at Mount Sinai, completing her PhD at the University of Cambridge through the National Institutes of Health-Oxford-Cambridge Biomedical Scholars Program. She also serves as Editor-in-Chief for the Roundtable Review, the online publication of Oxbridge Biotech Roundtable.

Patents, pharma and generic medicine

by
Dr Hayley Tyrer

Global drug pricing is a frequently debated issue worldwide, with a constant struggle between the needs of poorer nations, requiring cheaper, generic medicines, and the needs of pharmaceutical companies to sustain the profits from patented therapeutics that drive research into medicines of the future. The decision by the Indian Supreme Court earlier this year to reject patent approval and therefore allow the continued manufacture of generic forms of the leukaemia drug Glivec, patented by Novartis (1), has meant that once again the battle concerning global drug pricing has hit the media spotlight.

What are patents?

Patents are a legally binding form of intellectual property that protect novel inventions so they cannot be made, used, sold or distributed without prior permission from the patent holder (2). In exchange, details of the invention are made public. Drug companies in particular patent their products to prevent others from manufacturing cheaper versions of the same compounds. These patents usually last 20 years from the date of filing. However, drug companies can extend the lifespan of their products for a short period by obtaining new patents for existing compounds that have undergone some change that is sufficient to warrant a new patent. This lifespan extension is made possible by altering drug formulations or changing dosing regimens to improve the product – a process commonly referred to by anti-patent groups as 'evergreening'. Upon expiration of a patent, other firms are free to make cheaper copies of the same compound. Usually, the first company to challenge the patent has exclusive rights to produce the generic version for several months before other companies are able to do the same. This has the effect of driving down prices and results in more affordable medicines.

Patent controversy

There are both advantages and disadvantages to the current patent system. Advocates of the system maintain that patents are required to drive innovation forward. Specifically, they argue that patents help provide an incentive for economically efficient research and development and force disclosure of innovative ideas into the public domain. Conversely, critics of the system state that patents may actually hinder innovation, with patent litigation costs exceeding initial investment values for marketed compounds in some areas. Further, because of the large costs companies charge for their medicines, it has been suggested that patents are not consistent with free trade when poorer nations cannot afford the high prices set by some companies. In addition, the process of evergreening is contentious, with opponents saying that drug companies employ this strategy in order to charge higher prices for follow-on therapeutics that offer few additional benefits to patients. Indeed, a study in Geneva has shown that in a high-income setting evergreening strategies developed by pharmaceutical companies for follow-on drugs contributed to a substantial increase in overall healthcare costs (3). Pharmaceutical firms would perhaps argue that this process is required in order to compete with generic drug manufacturers and drive improvements to current medicines, in addition to generating profits to invest in research and development.

Glivec (Gleevec)

Current legislation known as the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) allows governing bodies within member countries to decide which pharmaceutical products should be protected by patents within their country, while protecting the intellectual property of other member countries. This allows more flexibility regarding the approval or denial of patents, importantly allowing governing bodies to take into consideration their country's own public health requirements.

India is one of the world's largest manufacturers of low-cost generic medicines. This year, the Indian Supreme Court ruled that a newly modified form of the anti-cancer drug Glivec (imatinib mesylate, also known as Gleevec in the US) would not have patent protection in India. This decision was made on the basis that the compound failed to meet set criteria enshrined in Indian patent law. Specifically, this form of Glivec was ruled to be not sufficiently different in terms of efficacy or composition compared to a previous version of Glivec already patented in the US, nor was it deemed to be in the public interest to grant a patent in India for this leukaemia drug. However, critics of this decision state that India did not afford patent protection to any pharmaceutical compounds until after 2005, which in itself may have violated international agreements on intellectual property (4). Novartis also professed disappointment with the decision, stating that: *"Glivec has been awarded patents in*

Figure 1: A typical Indian pharmacy (picture by Johanna Scheinost).

nearly 40 other countries, including China, Russia and Taiwan, but the Indian Intellectual Property Appellate Board (IPAB) is denying one for India. The IPAB acknowledges that Glivec satisfies the international requirements for novelty and inventiveness, but it does not find Glivec to meet the requirement under Section 3(d) of the Indian Patents Act of 2005. This act introduced a new efficacy enhancement hurdle for patenting new forms of known compounds. We believe that Section 3(d), the Indian legal paragraph intended as a hurdle for evergreening, should not be applicable to the breakthrough medicine Glivec, which has changed the lives of patients with rare cancers" (5).

Novartis further argued that the drug is not evergreening and that the price of the branded drug was not unaffordable, especially considering that the annual cost of treatment with generic imatinib is three to four times the average annual income. Further, Novartis voluntarily provide more than 95% of all Glivec patients in India with their medicine free of charge through the Glivec International Patient Assistance Program (GIPAP).

India is not alone in developing strict patent legislation that enables cheap medicines to be offered to those who need them. Other countries are following in a vein similar to that of India, with Argentina and the Philippines both having passed comparable legislation to restrict patents (1). Further, Brazil and Thailand have, for many years, been issuing compulsory licences for AIDS medication for public health reasons. International pharmaceutical companies are looking to gain a foothold in developing countries, seeking to generate sales through both the increase in demand that comes from additional markets, and through the higher rates of chronic disease in these places.

Ultimately this ruling in India may be a setback for these companies in their efforts to expand. This landmark ruling has demonstrated that patent law in India may end up becoming one of the strictest in the world and certainly favours the manufacturers of generic medicines. As several large patents come to an end and pharmaceutical companies undergo restructuring in these tough economic times, the battle lines between pharmaceutical and generic drug firms will be firmly drawn either side of patent law decisions.

References

1. Harris G & Thomas K (2013) Top Court in India Rejects Novartis Drug Patent. Available at http://www.nytimes.com/2013/04/02/business/global/top-court-in-india-rejects-novartis-drug-patent.html?pagewanted=all&_r=0 [Accessed June 2013].

2. Intellectual Property Office (© Crown copyright 2013) What is a patent? Available at http://www.ipo.gov.uk/p-whatis.htm [Accessed June 2013].

3. Vernaz N, *et al.* (2013) Patented Drug Extension Strategies on Healthcare Spending: A Cost-Evaluation Analysis. PLoS Med 10(6): e1001460.

4. Herrling P & Kilday LA (2013) India's Ruling on a Novartis Drug: 2 Perspectives. Available at http://www.nytimes.com/2013/04/13/opinion/indias-ruling-on-a-novartis-drug-2-perspectives.html?_r=0 [Accessed June 2013].

5. Novartis (2012) FAQ on the India Glivec Patent Case. Available at http://www.novartis.com/downloads/newsroom/product-related-info-center/faq-on-the-indian-glivec-patent-case.pdf [Accessed June 2013].

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Fighting for science: the *Science is Vital* campaign

by Dr David Yadin

In September 2010 the UK government was preparing to announce large spending cuts. Like many others, scientists waited anxiously to hear how they would be affected. There were strong indications that science funding would be significantly reduced. For cell biologist Dr Jennifer Rohn at University College London, this was a step too far. While others were resigned to their fate, she took action. "Let's march on London", she announced on her blog in September 2010 (1). The response to her post was overwhelming and initiated the *Science is Vital* campaign.

2010 Spending Review

When the coalition government came to power three years ago, its strategy was clear: cut spending and reduce the national debt. Budgets were only protected for areas deemed essential, including healthcare, schools and foreign aid. Funding for science appeared to be under threat. In the months preceding the government's spending review in late 2010, rumours abounded about the size of the proposed cuts, ranging from 25 to 40%. Business secretary Vince Cable MP gave a speech at Queen Mary, University of London outlining his vision for the future of science and engineering in the UK (2). Although he stated his support for "top class 'blue skies' research", he also suggested that academics should "collaborate with industry to maximise the benefit of their research" and that funding should be allocated to the most outstanding research, as judged by the Research Assessment Exercise (RAE), to "screen out mediocrity". According to the last RAE in 2008, this would only account for 54% of research groups in the UK.

The suggestion that scientists should have to do more for less was not well received. Cuts were likely to push the UK's science infrastructure, already under strain, to breaking point. Research group leaders would be able to hire fewer PhD students and staff, and it was feared that scientists would leave the UK for countries with better support for academic research. Several large-scale projects, such as the Diamond synchrotron in Oxfordshire and the UK's involvement in the Large Hadron Collider at CERN, would also be compromised (3). This would undermine years of previous investment. Many argued that rather than reducing science funding, the government should increase spending. Prior to the review in 2010, former MP Dr Evan Harris wrote that science "has a vital role in creating the economic growth we need to solve our problems" (4). The government's proposed cuts seemed short-sighted.

First campaign

Vince Cable's speech upset many people, but most had a fatalistic attitude to the looming cuts, according to Jennifer Rohn. Instead, she "got angry and fired off a blog post", declaring that it was time to take a stand (1). To her surprise, such was the level of support that the blog went offline due to the high volume of traffic. "I'd obviously struck a nerve", she said. The effort was supported by many prominent individuals and organisations including the *Campaign for Science and Engineering* (CaSE). A rally with around 2,000 participants was staged outside the Treasury in London a month later (Figure 1), and a petition calling for the government to protect science funding was presented to 10 Downing Street on 14 October 2010. It had 33,084 signatures, not only from scientists, but from people in many different professions ranging from plumbers and taxi drivers to stay-at-home mums. The government had no choice but to listen.

The *Science is Vital* campaign caused the coalition to rethink its plans. "Minister [for Universities and Science] David Willetts has publicly acknowledged that our campaign made a big difference. He set aside time to meet with us personally to discuss our concerns", said Dr Rohn. In the 2010 spending review, the science budget was frozen rather than cut, although this meant a reduction in real terms because of inflation. It was an important victory, but only the beginning of the campaign. After the first rally, *Science is Vital* became a formal group with an executive committee of volunteers chaired by Jennifer Rohn. In 2011, they held a panel discussion on science careers at the Royal Institution, which was attended by David Willetts. A report based on the session was subsequently delivered to the minister.

Time for a culture change?

The 2011 report highlighted problems that are all too familiar to those working in academic

science (5). One major issue is the shortage of jobs. "Statistics show that a permanent position awaits only 3.5% of PhDs", Dr Rohn told me. Another problem is the lack of career stability, particularly for post-doctoral researchers. It can be challenging for young researchers to make the transition to independent group leaders. Asked how the situation might be improved, Dr Rohn suggested that younger scientists could be allowed to apply for grants in their own right. "Often younger people's ideas go into their supervisors' grant applications, but they get no credit and are not spared if their short-term contract ends", she said. The report also highlighted the need for more permanent positions for experienced research staff who do not want to be group leaders. Ultimately, with the number of PhD-trained scientists far exceeding the number of available positions, students should be "actively encouraged to explore all the stimulating and varied science-related careers outside academia at an earlier stage".

Looking ahead: 0.8% funding target

On 26 June 2013, the government announced its spending plans for 2015-2016. Given the current weak state of the UK economy, further budget cuts were not surprising. Science funding was once again frozen, although the government pledged to increase investment in science infrastructure to £1.1 billion per year. *Science is Vital* is now pushing for an increase in the science budget. On 11 March 2013, a letter was published in the *Daily Telegraph* calling for an increase in "research and development spending to at least 0.8 per cent of GDP [Gross Domestic Product] – the G8 [Group of 8] average – to enable us to compete more effectively with the leading economies of the world" (6). It was signed by many leading academics, including Nobel Laureates. Current UK spending on research stands at around 0.6% of GDP, well below the averages of the G8 and European Union nations. An increase to 0.8% equates to an increase of approximately £2 billion. Public spending cuts are predicted to last until 2020, so this request may be unrealistic. "With the economy in such bad shape, it's a more difficult proposition than it was in 2010", Dr Rohn acknowledged. Nonetheless, the efforts of *Science is Vital* and others will help to keep hopes alive of improving the state of UK science.

How to get involved

Join *Science is Vital* for a mere £3.14 a year and attend their general meetings. Details can be found at http://scienceisvital.org.uk/. You can also contact Dr Jennifer Rohn personally to volunteer to help during their campaigns (jenny@scienceisvital.org.uk). And you can sign the GDP 0.8 petition online (http://scienceisvital.org.uk/2013/03/11/letter-in-the-daily-telegraph/) until the next general election. Encourage your friends and family to do the same and spread the word.

Figure 1: The *Science is Vital* rally in London on 10 October 2010 (picture by Joe Dunckley, http://www.flickr.com/photos/steinsky/).

References

1. Rohn J (2010) In which the great slumbering scientific beast awakens. Available at http://occamstypewriter.org/mindthegap/2010/09/08/in_which_the_great_slumbering_scientific_beast_awakens [Accessed June 2013].

2. Cullerne Brown W (2010) How to read Vince Cable's speech on science at Queen Mary's. Available at http://exquisitelife.researchresearch.com/exquisite_life/2010/09/how-to-read-vince-cables-speech-on-science-at-queen-marys.html [Accessed June 2013].

3. Ija A & Sample I (2010) UK scientists on collision course over £1bn research cuts. Available at http://www.guardian.co.uk/science/2010/aug/26/scientists-research-cuts-spending [Accessed June 2013].

4. Harris E (2010) Scientists must fight for their funding. Available at http://www.guardian.co.uk/science/blog/2010/aug/27/scientists-fight-funding-spending-review [Accessed June 2013].

5. Rohn J, *et al.* (2011) Careering Out of Control: A Crisis in the UK Science Profession? Available at http://scienceisvital.org.uk/2011/10/06/careering-out-of-control-a-crisis-in-the-uk-science-profession [Accessed June 2013].

6. Rohn J, *et al.* (2013) The Government must increase funding for science and engineering in order to boost growth. Available at http://www.telegraph.co.uk/comment/letters/9920713/The-Government-must-increase-funding-for-science-and-engineering-in-order-to-boost-growth.html [Accessed June 2013].

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Science communication: what's in a word?

by
Dr Elizabeth Hartfield

Communication /kəˌmjuːnɪˈkeɪʃn/ *(noun)* (1)

- *[mass noun]* the imparting or exchanging of information by speaking, writing, or using some other medium: *at the moment I am **in communication with** the journal that keeps rejecting my paper.*
- *[count noun]* a letter or message containing information or news: *an email communication.*
- the successful conveying or sharing of ideas and feelings: *there was a lack of **communication between** Pamela and her supervisor.*
- social contact: *she gave him some hope of funding his research project, or at least of their future communication on the matter.*

/kəˌmjuːnɪˈkeɪʃn/

Or, to put it more simply, *to share*. It sounds easy, but conveying complex scientific ideas can be more challenging than we first think.

Communication is all around us. Every day we write emails, be they scientific, professional or casual. We spend hours obsessing over figure alignments for scientific posters, and even longer over a single slide for an oral presentation at a conference that will appear on screen for less than a minute. We speak freely and easily to colleagues in highly specialist dialects, unique to our own labs. But once set free into the real world it can prove challenging to articulate your ideas even to someone working in a closely-related field, let alone to a lay scientist or your parents.

Picture the scene: Friday night at the pub and someone asks, "So, what do you work on?" You pause for a second, and you begin to tell them how technical, ground-breaking, complex and revolutionary your research is. Your enthusiastic monologue on how you plan to change the world, one protein channel at a time, draws to a close and you realise that your audience have glazed over and drained their pints. "My round then?" If this scenario is all too common to you then you need to consider the **golden rules of science communication:**

Why are you providing this information?

Who are your audience? What do they already know and how can they relate to what you are telling them?

What are your main messages?

What **tone** is appropriate? Think about the language, flow and sentence structure.

Getting the balance right is vital as engaging and maintaining an audience is key to successful communication. You need to make your research sound exciting, revolutionary and worthwhile. This is obvious to you, but your audience are a tough crowd and while you may often be faced with "So what?", enabling your audience to see the bigger picture will help them to put your research into perspective. Relating it to something that they know about will allow them to feel included, rather than intimidated by your fancy research project in the science lab. And by making the lab environment more accessible, you can keep the attention of your audience for longer. Try explaining how machines work in simplified terms. For example, a centrifuge spins tubes really fast, so everything inside the tubes goes to the bottom, in the same way that children taking a spin on a merry-go-round are pushed outwards.

One of the biggest hurdles that a scientist has to overcome is language. We throw terms around the lab such as centrifuge, Eppendorf, mutation. And then there are the acronyms: PCR, NMR, iPSC. These expressions may mean nothing to those outside of your immediate lab 'bubble' and can instantly turn an audience off. Try this activity for fun: can you explain your project using only the thousand most used words? It's not as easy as you might think! Visit http://splasho.com/upgoer5/ to have a go.

The key to improving your communication skills is practice. Find yourself an audience: give talks to lay scientists, take part in science fairs and attend communication workshops. These are great opportunities to communicate your science to people who have no idea what you are working on. If you explain your research to as many different audiences as possible, you will quickly learn what works, and what doesn't. By describing your research in an accessible way, you will be able to quickly convince your audience why you are excited by your science, and why they should be too. Further, through increasing awareness we can reach out and get more people involved in supporting the scientific community as a whole.

References

1. Adapted from Oxford Dictionaries. Available at http://oxforddictionaries.com/definition/english/communication [Accessed June 2013].

Dr Elizabeth Hartfield is a Career Development Fellow in Dr Richard Wade-Martins' laboratory, Oxford Parkinson's Disease Centre, Department of Physiology, Anatomy and Genetics.

Angelina Jolie: genetic inheritance and medical choice

by Andrew Douglas

I have a lot of time for Angelina Jolie. Back in 2001, as the movie heroine of *Lara Croft: Tomb Raider*, I remember thinking (rather judgmentally) that she would turn out to be yet another manufactured, one-dimensional Hollywood star, chosen more for her looks than her ability to act, and that her film career would not amount to much more than a brief flash in the pan. However, I have had to rethink this harsh assessment, as she has increasingly been using her privileged position to campaign for important humanitarian issues around the world.

BRCA1

With great power comes great responsibility, and arguably the same can be said of great fame. It is therefore commendable that a star such as Angelina Jolie should publicly announce that she has had a prophylactic bilateral mastectomy to reduce her breast cancer risk (1). The *BRCA1* mutation she carries confers a lifetime risk of breast cancer of between 60-85% in affected women (2). These *BRCA1*-related cancers tend to be aggressive in nature and often affect women in their 40s or 50s. In addition, there is a lifetime risk of 40-60% for ovarian cancer. A gene mutation carrier has a 50% chance of passing on the same faulty gene to each child and it is usual to find affected families with several female relatives across multiple generations with these cancers. Men are just as likely to inherit the mutation, but have a much lower breast cancer risk than women, although there may be some increased risk of prostate cancer.

Treatment options

For women found to have a *BRCA1* (or a related *BRCA2*) mutation, there are two main treatment options. The first is to undergo regular breast screening through annual mammography and MRI scanning allowing early detection and treatment of cancers. Such screening is effective and many women in this situation opt for it in the knowledge that although they are likely to develop a cancer at some point, it will be dealt with before it has a chance to spread. The alternative is to have a bilateral mastectomy to remove the breast tissue. While this is the surest way to reduce one's risk, it is a major surgical operation with associated risks. The choice between screening and surgery is deeply personal, and a patient's own experience of breast cancer, whether personally or within the family, is likely to play a significant role in her decision. For ovarian cancer, studies have not found any prognostic benefit from ultrasound screening combined with blood measurement of ovarian tumour markers (3). Most women carrying *BRCA1/2* mutations therefore choose to have prophylactic removal of the ovaries and fallopian tubes once they have completed their families.

In making her story public, Angelina Jolie hopes other women will become aware of their options in managing their breast cancer risk. The implication would appear to be that women should seek genetic testing for *BRCA1/2* mutations. However, a number of factors limit the utility of genetic testing as a population-wide screening tool. Aside from the issue of finite NHS resources, there is a limited ability of clinicians to interpret genetic sequencing data without the context of an affected proband and relevant family history. Despite great advances in our understanding of genetics in recent years, there are still many new sequence variants, even in well-studied genes, the effects of which remain unknown. Discovering such variants in unaffected patients without a family history of breast or ovarian cancer has the potential to create confusion, anxiety and uncertainty. Genetic testing is often portrayed as a black-and-white answer, but in many cases the reality is much more grey. Through all of this, one's family history remains the best guide to one's own risk of familial cancer. So, rather than reaching straight for the direct-to-consumer genetic testing kit, it may instead pay dividends for us to consider our own family histories. Only in the light of our families can we properly interpret our genetic inheritance and make a truly informed medical choice.

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References

1. Jolie A (2005) My medical choice. *New York Times*. Available at http://www.nytimes.com/2013/05/14/opinion/my-medical-choice.html?_r=0 [Accessed June 2013].
2. Lalloo F & Evans DG (2012) Familial breast cancer. *Clin Genet* 82(2):105–114.
3. Stirling D, *et al.* (2005) Screening for familial ovarian cancer: failure of current protocols to detect ovarian cancer at an early stage according to the international Federation of Gynecology and Obstetrics system. *J Clin Oncol* 23(24):5588–5596.

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RESEARCH HIGHLIGHTS

by Anna Sigurdsson

Twigg SR, *et al.* (2013), *Human Molecular Genetics* 22(8):1654–1662.

Cellular interference in craniofrontonasal syndrome: males mosaic for mutations in the X-linked *EFNB1* gene are more severely affected than true hemizygotes.

Craniofrontonasal syndrome (CFNS) is an X-linked disorder caused by loss-of-function mutations in *EFNB1*, the gene encoding the membrane protein EPHRIN-B1. Interestingly, unlike most X-linked diseases, heterozygous females account for the majority of cases and are more severely affected compared to hemizygous males. Female phenotypes include frontonasal dysplasia, craniosynostosis (premature ossification of the infant skull) and additional minor malformations, whereas the only symptom in typical male cases is ocular hypertelorism (increased distance between the eyes).

This paradoxical reversal in phenotypic severity between sexes may be explained by X-inactivation and male sparing, due to redundancy in the essential functions of EPHRIN-B1. In female CFNS patients, X-inactivation leads to functional mosaicism for cells with a differing expression of EPHRIN-B1, resulting in the generation of abnormal tissue boundaries. This process, known as cellular interference, cannot occur in hemizygous males. However, it has been found that some men exhibit more severe symptoms, similar to the female CFNS phenotype. This study hypothesised that these individuals, who clearly do not fit with the cellular interference model for CFNS pathogenesis, might be somatically mosaic for *EFNB1* mutations, as this would create a situation analogous to typical female CFNS.

The group investigated tissue samples from six sporadically presenting males and could identify different combinations of mosaic mutations of *EFNB1* in all cases, with levels of mutant cells ranging between 15% and 69%. Three missense changes were found, as well as two gene deletions. A novel point mutation in the 5' untranslated region was also detected, which mutates the stop codon of a small upstream open reading frame (uOFR). Using a dual-luciferase reporter construct, this point mutation was found to exacerbate interference with translation of the wild-type protein. This mechanism – the predicted translational read-through of a conserved uORF, repressing the translation of *EFNB1* from the main downstream open reading frame – was a novel discovery. These findings demonstrate that male mosaics in an X-linked, dominant disorder present a more severe outcome than hemizygote males. It also provides support for the cellular interference mechanism, which is normally related to X-inactivation in females.

Beggs AD, *et al.* (2013), *The Journal of Pathology* 229(5):697–704.

Whole-genome methylation analysis of benign and malignant colorectal tumours.

Epigenetic modification of DNA has been increasingly recognised as an important factor in carcinogenesis. Changes in DNA hypomethylation and hypermethylation are associated with the progression of colorectal cancer, particularly during the progression from normal mucosa to adenoma and to carcinoma. However, little focus has been placed on genome-wide methylation and how it affects colorectal cancer, with most research to date being limited to the study of individual CpG islands.

In this study, Beggs *et al.* aimed to identify a pattern in changes of methylation in colorectal cancer. The group carried out a whole-genome methylation analysis of paired colorectal cancer and normal tissue samples, as well as colorectal adenomas. They found that over 2,000 genes were differentially methylated. Of these, *ATM* was the highest-rated gene exhibiting differential methylation between carcinomas and adenomas. The highest-rated individual gene for differential methylation in both carcinomas and adenomas versus normal tissue was *GRASP*, which encodes the general receptor for phosphoinositides-1-associated scaffold protein. The group suggests that differential methylation of this gene might be a potential biomarker for colorectal cancer.

Methylation was also shown to occur in the Netrin-DCC and SLIT-ROBO molecular pathways. Moreover, widespread methylation was shown in the progression from adenoma to carcinoma, rather than in the transition from normal tissue to adenoma. The group also found that hypomethylation occurred during the progression from normal tissue to adenoma, whereas hypermethylation is primarily associated with the transition from adenoma to carcinoma.

OXFORD UNIVERSITY BIOCHEMICAL SOCIETY

Welcome!

Welcome to the new academic year! The Oxford Biochemical Society (OUBS) is the official Department of Biochemistry student association and social network. The Society invites outstanding speakers from outside Oxford to give lectures in the Department. These talks attract students, post-docs and senior members from all of the various life-science departments of Oxford University. We are student-run and also host a wide range of exciting events for graduates and undergraduates.

Annual careers day fair

Lectures by world-class scientists

Meetings every two weeks

Group outings, social hours, events, study sessions, discussions and more!

Check out our website at **www.bioch.ox.ac.uk/oubs** or contact the committee at **oubs@bioch.ox.ac.uk**.

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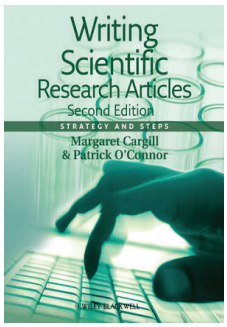
BOOK REVIEW



Writing scientific research articles: Strategy and steps, 2nd Edition

Margaret Cargill and Patrick O'Connor

ISBN: 978-1-1185-7070-8, Wiley-Blackwell (2013), Paperback, 236 pages, £19.99

Reviewed by Amy Baxter

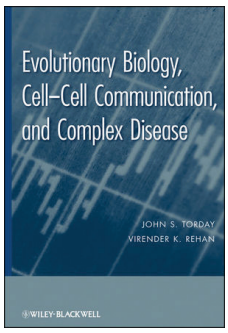
In this period of recession and funding cuts, it has never been more important to get high-quality papers published in the top journals. *Writing Scientific Research Articles* is a workbook that aims to assist the author of a scientific paper through every step of the publication process, from writing to submission, and even dealing with rejection and resubmission.

Writing Scientific Research Articles is broken down into four main sections; the second focuses on writing an article and the third on getting manuscripts published. The fourth section aims to address more advanced and specific aspects related to article publication, such as arranging Journal Clubs and writing funding proposals. There is also a chapter on writing articles with English as an additional language, which may be useful for international writers.

The book is designed to be flexible in its use and can be worked through in multiple ways. It can be used in parallel with paper writing, helping the reader to choose a title and to design appropriate figures, for example. In addition, there are short tasks and exercises to work through every few pages, without a specific paper in mind. Specimen paragraphs and phrases are provided to help with their completion. Furthermore, examples of full papers are provided at the back of the workbook to use in some of the tasks.

It is important to note that each scientific discipline will have its own standards and expectations, most commonly in terms of layout and structure. While the authors attempt to cover most disciplines, there is an obvious bias towards basic biology (O'Connor's speciality). If working in a different field, it would be helpful to work through the book with a few well-written papers in your subject area to note any specific differences and common themes particular to your field.

Writing Scientific Research Articles is a helpful resource that can be worked through as a whole, or used as a reference when advice on specific problems is required. Its step-by-step approach makes the experience of paper writing less daunting. However, as the authors note, perhaps the best resource is colleagues who have experienced the highs and lows of peer-review firsthand.



Evolutionary Biology, Cell-Cell Communication, and Complex Disease

John S. Torday and Virender K. Rehan

ISBN: 978-0-470-64720-2, Wiley-Blackwell (2012) Hardback, 192 pages, £55

Reviewed by Anna Sigurdsson

The aim of *Evolutionary Biology, Cell-Cell Communication, and Complex Disease* is to conceptualise and understand the process of evolution by focusing on the cell as the smallest functional unit of biology and by following the progression from unicellular to multicellular organisms.

The book is neatly structured into 10 chapters, each of which is logically divided into shorter subsections. Most chapters begin with a glance back at the history of theories relating to the chapter, for example references to Charles Darwin's or E. O. Wilson's views on different aspects of evolution, which transitions into the main text of the chapter. At the end of most chapters there is a brief summary to reinforce the main message of each chapter, and it is a shame that this is inexplicably omitted from some sections. At the end of each chapter there is also an introduction to the next one, which contributes to the logical construction of the book's argument, linking the chapters together nicely.

The first chapters of the book cover the most fundamental aspects of the topic, describing the cellular origin of vertebrates and the evolution of mechanisms for cell-cell communication (e.g. lipid rafts). Later chapters explain how these mechanisms are integrated into other processes, such as *cis*-regulatory mechanisms, finally linking the evolution of cell-cell signalling to problems in clinical medicine. The authors argue that this approach can, and should, be applied to the practice of clinical medicine.

The book is clearly targeted at an audience with a relatively good knowledge of biology and an academic interest in cell-cell communication, evolution and lipid metabolism. Despite this the writing style is straightforward, making the book more accessible to those with less expertise in this quite specific field. Moreover, the authors provide brief but helpful explanations of relevant concepts and theories along the way, making it easy to follow the main arguments. The text is complemented with a number of explanatory figures of the models being described, and although an untrained eye is not necessarily able to interpret all of the figures, the captions are very clear and helpful.

Overall, this book provides an interesting and forward-thinking view of complex disease described from the integrated perspectives of cell-cell communication and evolutionary biology. I would warmly recommend it to anyone who is interested in this field and looking for an easy-to-read yet quite technical book with a novel perspective.

Tag-based Next Generation Sequencing

Edited by Matthias Harbers and Günter Kahl

ISBN: 978-3-527-64457-5, Wiley-Blackwell (2011)
Hardback, 608 pages, £150

Reviewed by Evan Harrell

Next Generation Sequencing (NGS) technologies have drastically reduced the prohibitive costs and long wait times formerly associated with large-scale 'omics' studies, at the same time generating enormous amounts of bioinformatics data. As the costs have come down, many very specialised NGS-based approaches have been conceived to study very specific biological applications. *Tag-based Next Generation Sequencing* provides an in-depth insight into many of these applications.

The book is divided into three parts. In the first section, each chapter presents a very detailed explanation of the most recently developed tag-based experimental techniques, including step-by-step laboratory protocols, as well as advice on setting up experiments that will produce informative results. Having carried out many NGS-based experiments myself, this kind of information can prove vital. It also gives the experimenter an idea of the limitations of whichever approach they choose to take.

The second section of the book highlights a few of the so-called 'third-generation' sequencing approaches, which are more focused on obtaining longer reads from fewer sample molecules. These techniques are more likely to come into play in the near future, but are important to have in mind when thinking about sequencing approaches.

Finally, the third section conveniently comprises a few chapters providing general information and guidance in selecting NGS-based experimental approaches, understanding the bioinformatics involved in data analysis, and even offering technical reviews of the statistics involved in large-scale 'omics' studies. With easy-to-understand criteria and cross-platform analysis of competing experimental paradigms, this section is an absolutely essential read before deciding on which experimental approach to take.

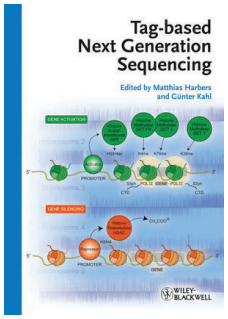
Since the book is compiled as a compendium of NGS-based techniques written by each respective group of discoverers, there is high redundancy in general technical description across chapters. At times the book almost feels like a marketing catalog for NGS-based approaches, as one would expect considering that it is only natural for the inventor of a technique to encourage its mass application. Overall, the book is a very useful resource from which you can gain an understanding of the plethora of existing NGS tag-based approaches in this fast-moving field.

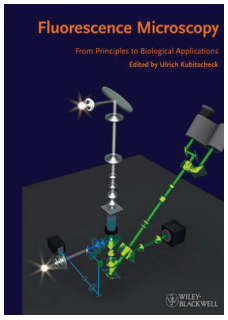
Fluorescence Microscopy: From Principles to Biological Applications

Edited by Ulrich Kubitscheck

ISBN 978-3-527-32922-9, Wiley-Blackwell (2013)
Hardback, 539 pages, £100

Reviewed by Stuart Thomas





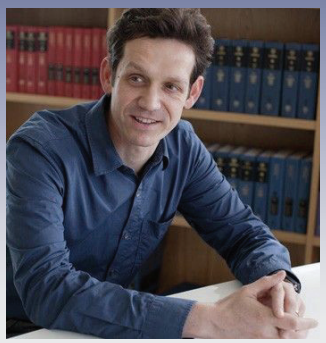
I admit to having a natural prejudice against books written by experts in their fields yet edited by one academic. It can work when each chapter focusses on very different aspects of a topic: if chapters are self-contained essays, then an editor can put them in a suitable order. However, if chapters build upon each other then the book needs to be tightly edited. In my (limited) experience, textbooks like this tend to be loosely edited and poorly stitched together. So it is with *Fluorescence Microscopy*.

Chapters tend to contain similar descriptions and diagrams that have been included earlier in the book. For example, both the second chapter (Principles of Light Microscopy) and the third chapter (Fluorescence Microscopy) have detailed descriptions of electron excitation during fluorescence, a significant overlap. The preface gives the reason behind this as being "to maintain the argumentation in these chapters" when experienced readers skip the introduction. However, this is only acceptable in a book with easily readable chapters. Although each section is extremely well researched and comprehensive, they do not scan easily. Too much in-depth knowledge is presented on every page. A specialised book like this, if it is to be read by students as intended, needs to draw in the reader; beginning with basics, then explaining in more detail. Instead, even the first chapters deal with the fundamental elements of microscopy in a highly comprehensive manner.

However, as a reference book, *Fluorescence Microscopy* can be very effective. For a reader already comfortable with some of the material, each chapter can be used as a go-to guide. This is the true purpose of the book, to be "studied according to interest and requirement". Chapters include formulas and theories usually omitted from books on this topic, and someone already comfortable with microscopy can easily increase their knowledge and develop a deeper understanding of general microscopy theory. The later chapters dealing with confocal microscopy, FRET, super-resolution and other advanced fluorescence techniques are similarly meticulous and thorough.

In short, if you already have a sound knowledge of fluorescence microscopy then this textbook can greatly increase your understanding of this topic or be used as a reference. If you're a student or are beginning to learn to use microscopy in your work then I'd recommend putting this back on the shelf.

5' with... Prof Scott Waddell



Prof Scott Waddell is a Professor of Neurobiology and a Wellcome Trust Senior Research Fellow in Basic Biomedical Science, based at the Centre for Neural Circuits and Behaviour. After obtaining his PhD in cancer biology, he radically changed fields and moved to the US to study learning and memory in fruit flies, in the laboratory of Prof Chip Quinn at the Massachusetts Institute of Technology (MIT), and has never looked back! He continued his prolific academic career in neuroscience as a research group leader in the Department of Neurobiology at the University of Massachusetts Medical School for 10 years before moving to Oxford in 2011.

Interviewed by Clara Howcroft Ferreira

When did you first decide you wanted to be a scientist?
I stumbled into science, but I guess I was inspired to consider being a scientist by my high school chemistry and biology teachers. My chemistry teacher, the late Kenny Ward, had a particularly special gift for making everything interesting.

If you weren't a scientist, you would be…
I would be an artist, a mountain guide, and have a serious go at ultra distance sports: running, biking and swimming. I'd do all of these things at once!

What was your worst disaster in the lab?
In the grand scheme of things, nothing in the lab is a disaster. I did many stupid things, some of them on purpose, and I learned from them all.

What has been the most memorable finding of your career so far?
I am continuously amazed by the wonder of biology. Every discovery is memorable – for the moment and for the people involved.

What is the best advice you have ever received?
Just say no. As a young scientist you are inclined to say yes to every bureaucratic request. Running a lab needs energy, focus and time. I would give the same advice, but I would also suggest you do something you are genuinely interested in and not what someone else tells you.

Do you have a favourite classical experiment?
If you ask me this again in a week's time, I'll give you a different answer! Several years ago I would have said something involving molecular biology. However, in this current era of experiments involving brain stimulation it is hard to overlook the classical work of James Olds and Peter Milner (1954) in defining the reward systems in the rat brain - the initial observation happening by chance and noticed by a keen eye and open mind.

Remaining on a behavioural slant, for experimental craft and artistry there are few better examples than the work of Vincent Dethier. Every chapter in his classic book The Hungry Fly (1976) contains an ingeniously designed experiment.

In your opinion, what makes a good scientist?
An open mind, a lack of fear and the desire and courage to stick your neck out and say something that challenges current thinking.

How do you imagine biological research will change over the next 20 years?
Things have already become more multi-disciplinary, information-dense and mathematical. This will continue and I think the challenge remains in interpreting the enormous data sets, distilling the salient points and explaining them with clarity. It will also become more important to consider lab findings within a more ecologically relevant framework.

Write for *Phenotype*?

- The deadline for article submissions is Friday of 8th week, 6 December 2013
- We accept articles on any aspect of biological sciences research, books or science education
- Articles can be either 650 or 1300 words

If interested, please get in touch: oubs@bioch.ox.ac.uk.

Work for *Phenotype*?

If you'd like to get involved in editing, production or management of *Phenotype*, please get in touch: oubs@bioch.ox.ac.uk.

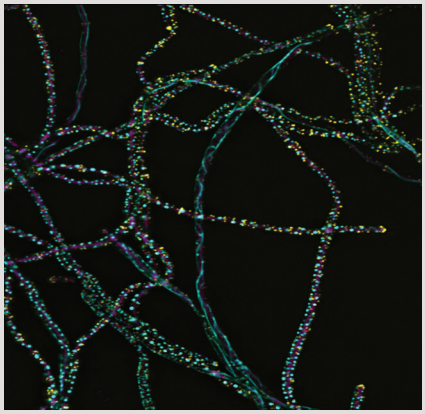
SNAPSHOT Research Image Competition

This issue's winner is...

Sheng-Wen Chiu

Sheng-Wen is a 4th year DPhil student in the Department of Biochemistry, co-supervised by Prof Judy Armitage and Prof Mark Leake.

The winning image of the bacterium *Rhodobacter sphaeroides* was captured using 3D fluorescence deconvolution microscopy. It shows the chemosensory protein clusters at the membrane (tagged with YFP) and the cytoskeletal protein FtsZ (tagged with CFP) in filamentous cells. The differential interference contrast image was pseudocoloured purple.



Sheng-Wen became fascinated by the spatial organisation of cells during his BA and Master's degrees obtained at the Department of Microbiology, Soochow University in Taiwan, where he studied bacterial cytoskeletal proteins. He subsequently moved to Oxford for his DPhil to further his investigations in this field.

He utilises the complementary expertise of Prof Judy Armitage (Department of Biochemistry) and Prof Mark Leake (Department of Physics). The Armitage group investigates the dynamics of bacterial sensory transduction and the control of bacterial motility, whilst Mark Leake specialises in developing and applying novel forms of optical microscopy to investigate complex biological processes at the level of single molecules. Sheng-Wen uses single-molecule, super-resolution fluorescence microscopy to obtain integrative data with high spatial and temporal precision in order to visualise the working of cytoskeletal and chemosensory proteins in living *R. sphaeroides* cells. By doing so, Sheng-Wen hopes to acquire the information for the dynamic localisation, stoichiometry and architecture of these proteins to develop a systems-level *in vivo* biochemical understanding of bacterial spatial regulation.

Chemotaxis and cell division are vastly different cellular activities. However, both require the assembly of several molecular complexes at spatially distinct locations in the cell. The proteins involved in chemotaxis must be coordinated with cell division to ensure that each daughter cell inherits a complementary set of chemosensory proteins. Sheng-Wen's work focuses on how cytoskeletal proteins FtsZ (a tubulin homologue), MreB (an actin homologue) and ParAB (proteins involved in DNA segregation in bacteria) contribute to the positioning of chemosensory proteins during the cell cycle.

Previous studies in *E.coli* suggested that membrane chemosensory clusters are positioned, either by stochastic self-assembly or with the help of cytoskeletal proteins, at distinct cellular locations and distributed to each of the daughter cells during cell division. By using high-resolution imaging of cytoskeletal and chemosensory proteins, Sheng-Wen found that this was not the case in *R. sphaeroides*. Chemosensory proteins are localised in large unitary clusters that move randomly along the cell membrane, rather than being actively positioned at cytokinetic sites. Sheng-Wen and his colleagues therefore propose that the positioning of chemosensory clusters relies on cell geometry and simple diffusion rather than active positioning. He also found that FtsZ forms different assemblies and develops into the cytokinetic Z-ring via a previously undiscovered pathway. The nature of these assemblies is Sheng-Wen's current endeavour in the lab.

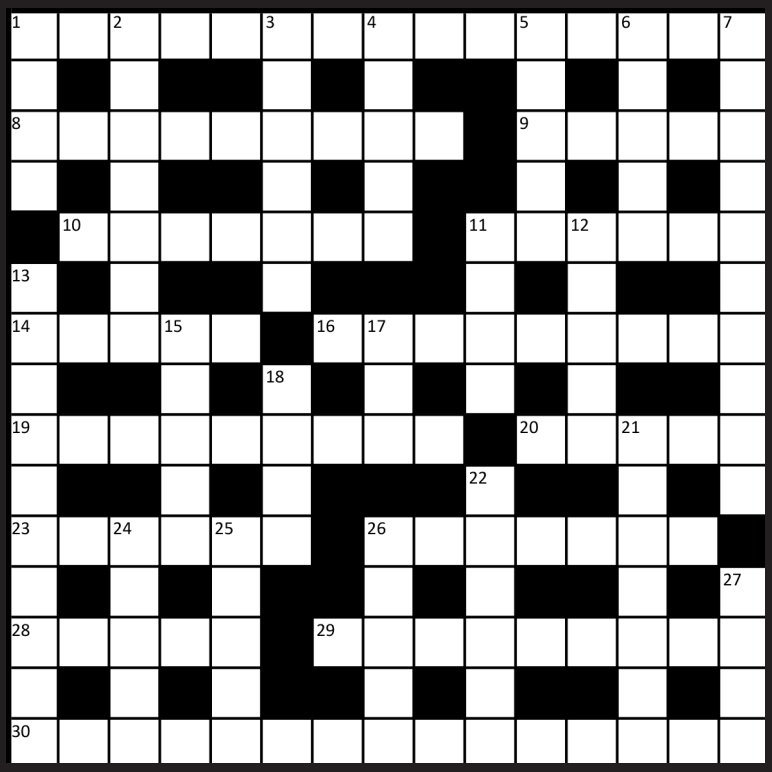
Win a £50 book voucher kindly provided by Oxford University Press!

Do you have an image from, or inspired by your research? Why not enter it in SNAPSHOT?
We are now accepting entries for pictures to be featured on the cover of *Phenotype* HT 2013/14.
To enter, send images to oubs@bioch.ox.ac.uk with a brief description (maximum 100 words).
Please get permission from your supervisor before sending any images. There is no limit to the number of entries per person.
The deadline for the competition is 6 December 2013.

PHENOTYPE crossword

Enter the competition by sending your answers to oubs@bioch.ox.ac.uk or leave a paper copy in a sealed envelope in the OUBS pigeonhole at the New Biochemistry reception. Entries received by 20 December 2013 will be entered into the prize draw.

We are pround to introduce our new cryptographer, *Fish*, who challenges *Phenotype* readers to crack this cryptic crossword on the theme of molecular biology.



The winner can choose one of the four books reviewed in this issue, generously provided by Wiley-Blackwell.

WILEY-BLACKWELL

Across

1 It'll help the anion left by pH change show it? (15)
8 To 7 27s or 19 with 12 and 1ac, 3 or 30, perhaps; it's said to be in short supply! (9)
9 Delicate jewellery at cinema (5)
10 Between one French and German, very unstable (7)
11 Plea for publicity for headless chicken (6)
14 It spins backwards and forwards? (5)
16 Obfuscate and lie about twitch, but it's still the same (9)
19 Salad oil mixed with 1000 plant compounds (9)
20 Donkey stores copper in spore sac (5)
23 Scoundrel wraps greek letter in a proteinacious covering (6)
26 Starts or backs in transcriptional units (7)
28 Radiation from Uranium City results in dangling flesh (5)
29 Quiet! That man has new prediction about first of remarkable events (9)
30 Indicator shows right; phone Bloom about colour (11,4)

Down

1 The heart of the matter: the stone is hot (4)
2 Taken in by sex tincture - it'll kill us all! (7)
3 Indicator shows left; it's holding up mum (who loses her head) (6)
4 Heartless greeting and zero credentials - it's a bone in my throat! (5)
5 Resinous stop codon? (5)
6 Appreciate delegate who exchanges letter (5)
7 Nervous looks, they say, take time to counteract . . . (10)
11 . . . prions destroying neuritic core in brainstem (4)
12 500 placed in account is from proton donors (5)
13 It coats fish stuffed with mixed curd and a basil tip? (10)
15 Stop codons have no friends (5)
17 Father sung three-note harmony (3)
18 Invalidate space (4)
21 Harden anthracite by adding nitrogen, germanium (7)
22 Star sign holds worker in shack (4,2)
24 Even opal auction is held on dwarf planet (5)
25 Adult insect is folding paper, flipping it and cutting inner edges (5)
26 Stop codon does chore work (5)
27 Graduates on drug are vulgar (4)

Congratulations to Joel Beevers from DPAG who won the Trinity 2013 crossword competition.

Answers to the crossword from issue 15 (TT2013)
Across: 9 masseur; 10 hominid; 11 erotogenic; 13 Epsom; 14 hobbit; 16 clot; 19 tarp; 20 aswarm; 21 pause; 23 reasonable; 27 raiment; 28 gadwall; 29 California poppy
Down: 1,1A Homo heidelbergensis; 2 inscribe; 3 erect; 4 borage; 5 rehandle; 6 Eumycetes; 7 sane; 8 sodium pump; 12 phosphoric; 15 interleaf; 17 ergaster; 18 gall wasp; 22 Mowgli; 24 add up; 25 vial; 26 flay