PHENOTYPE

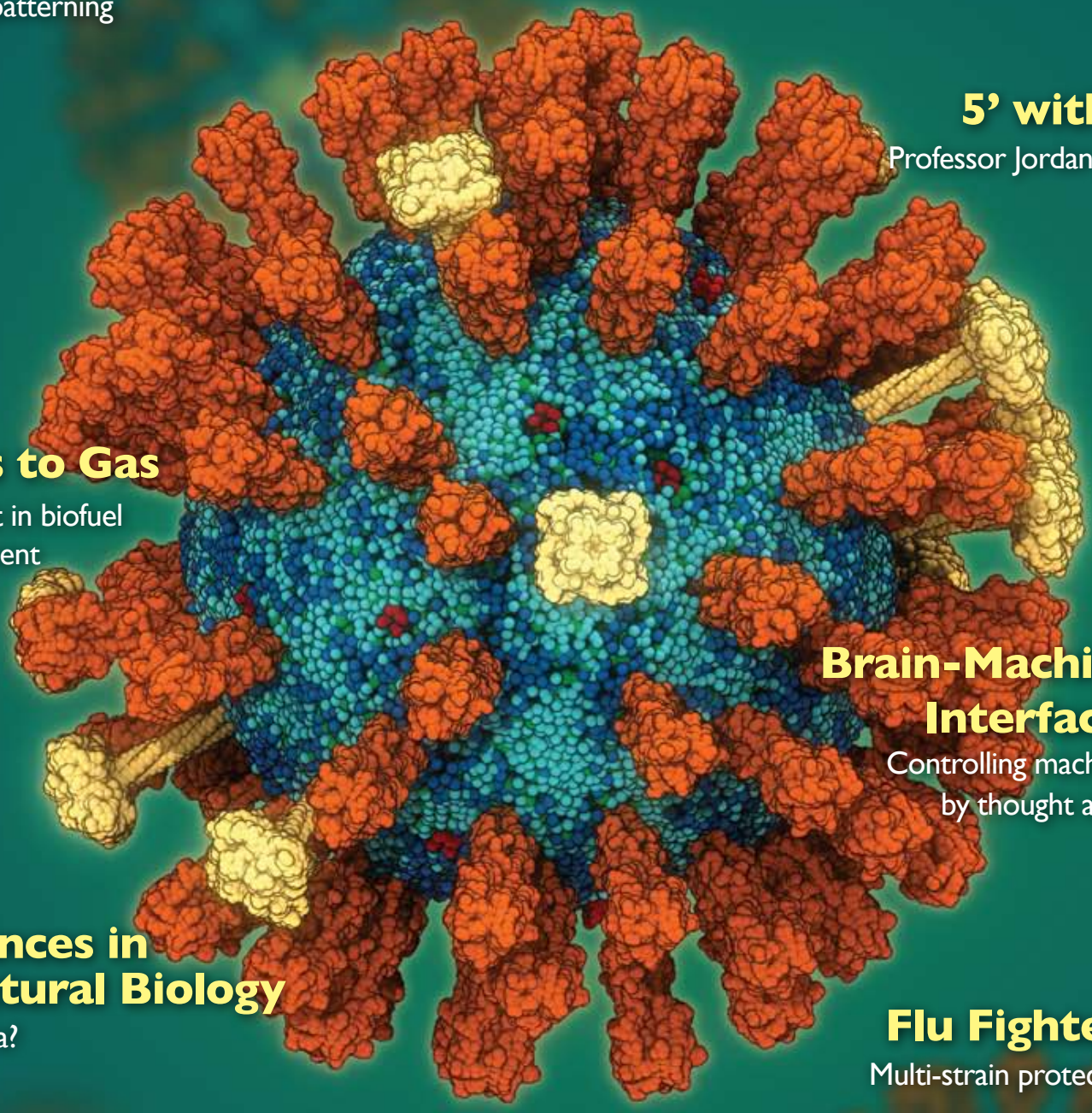
Issue 9, Trinity Term 2011

Research Highlights

HIV vaccine development
Cell division in archaea
Next generation solar cells

Mammalian Embryogenesis

Dr Shankar Srinivas discusses anterior patterning



5' with...

Professor Jordan Raff

Grass to Gas

The latest in biofuel development

Brain-Machine Interfaces

Controlling machines by thought alone

Advances in Structural Biology

A new era?

Flu Fighters

Multi-strain protection

PLUS...

Bioremediation
Science in the Media
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EDITORIAL

Phenotype is published by the Oxford University Biochemical Society.

Welcome to the 9th issue of *Phenotype*! This issue marks the completion of *Phenotype's* third academic year and, I hope you agree, the magazine continues to go from strength to strength. It has been a pleasure to act as the fourth *Phenotype* Editor.

A highlight of this issue is our feature article written by University Lecturer Dr Shankar Srinivas who writes about his research on anterior patterning during mammalian embryogenesis. Also featured is an interview with Professor Jordan Raff, a leading name in centrosome research and, within the Dunn School at least, in the instigation of snow ball fights!

In the *Features* section, Narin Hengrung introduces the Linac Coherent Light Source, the brightest X-ray laser ever produced. Recent 'proof-of-principle' experiments indicate that this technology could allow large protein structures to be determined without the need for crystallisation, potentially opening the door for real-time single-molecule structural analysis. Understandably, this is causing much excitement amongst researchers. If the technology lives up to its promise, it could revolutionise the field of structural biology.

Furthermore, Dr Carinne Piekema describes the almost unbelievable work thus far in developing a brain-machine interface. She explains how and why scientists, engineers and neurosurgeons are developing technologies that could one day lead to robot armies controlled by thought alone! On a more down-to-earth note, Dr Sarah McKim brings us up to date with the exploitation of non-food crops for biofuels and, inspired by the *Deepwater Horizon* oil spill, Penny Sarchet reflects on the challenges involved in applying bioremediation to the open ocean.

In our ever-popular *Science and Society* section, Lisanne Stock discusses the problems encountered when representing science in the mainstream media and, in response to the Ghost Forest article published in Issue 8, Dr Gabriel Hemery from local charity the Sylva Foundation describes their work to promote sustainable forestry within the UK.

Last issue's *Snapshot* winner was Daniel Parton who received a £50 book voucher prize generously provided by our sponsor Oxford University Press. His stunning simulations of the influenza virus envelope are shown on the front cover, and you can find out the science behind his image on page 31. If you have an image inspired by your research, why not enter our next *Snapshot* competition? We are also running our crossword competition again, sponsored by Wiley Blackwell. Enter for your chance to win one of the books reviewed on page 25.

As ever, this issue is a result of huge efforts from all members of the *Phenotype* team; thank you for making my job easy. If you would like to get involved with *Phenotype*, be that in writing, editing, design or promotions, do please get in touch via oubs@bioch.ox.ac.uk.

We hope that you enjoy the issue!

Dr Tamzin Gristwood
Phenotype Editor
Dunn School of Pathology

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Issue 9

CONTENTS

Trinity 2011

OUBS SEMINARS

Tuesday 3rd May
Dr Joao Pedro de Magalhaes
Institute of Integrative Biology, University of Liverpool
"Integrative genomics of ageing: New approaches for an 'old' problem"

Monday 9th May
Dr Ian Collinson
School of Biochemistry, Bristol University
"Structure of the bacterial translocon activated by pre-protein"

Monday 16th May
Dr Adrian Mulholland
Centre for Computational Chemistry, Bristol University
"Computational enzymology: modelling biological catalysts"

Tuesday 31st May
Professor David Jones
Department of Computer Science, University College London
"Gaining biological insight from disorder: natively unfolded proteins in the human genome"

Monday 6th June
Professor Steve Busby
School of Biosciences, University of Birmingham
"Regulation at simple and complex bacterial promoters"

OUBS FEATURED SEMINAR:
Monday 13th June
Dr Steve West
Cancer Research UK - London Research Institute
"Regulatory control of recombination-mediated DNA repair and links to cancer"

Monday 20th June
Professor Stephan Sigrist
Institut für Biologie, FU Berlin
"Shedding light on the assembly of synapse structure and function"

Tuesday 21st June
Dr Lizzie Burns
Science to Life
Title to be confirmed

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

MANAGING DNA DAMAGE

This term, OUBS hosts the well-known cancer biologist, Dr Stephen West. Dr West read for his degree and doctorate in Newcastle. He then pursued postdoctoral work at Yale before returning to the UK to continue his research interests in London. His work in cancer biology has led to numerous awards and distinctions, including the Biochemical Society Novartis Medal and Prize (2008) and the Louis-Jeantet Prize for Medicine (2007). He is a Fellow of the Royal Society (FRS), a Fellow of the Academy of Medical Sciences (FMedSci), and a member of the European Molecular Biology Organisation (EMBO). He is currently the Deputy Director and a Senior Group Leader at Cancer Research UK's Clare Hall Laboratories.

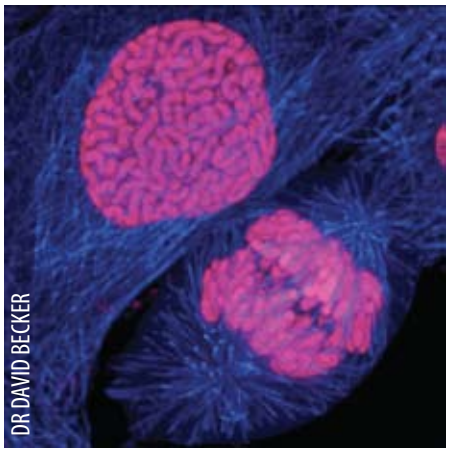
A main theme of the research conducted at Clare Hall is genome integrity, encompassing chromosome biology, cell cycle dynamics and DNA repair. Genome instability has been called "an evolving hallmark of cancer", as it often gives rise to mutations that can promote cancer progression (1). Dr West focuses on how cells use DNA recombination to promote stability and decrease mutations, with a long-term view to finding potential therapeutic targets. His laboratory is specifically investigating how chromosomal breakage is managed by the cell.

In eukaryotes, homologous recombination (HR) is important in somatic cells for the repair of damaged or broken chromosomes via double-strand break repair (DSBR). DSBR occurs during the S and G2 phases of the cell cycle, when chromosomes have replicated but not yet divided. The region either side of a double-strand break is first excised, after which the defective chromatid exchanges strands with its undamaged sister. After HR, each sister chromatid is made up of an intact strand and a gapped strand. This gap is then filled using the intact strand as a template, resulting in two undamaged chromatids. A defective DSBR mechanism often results in unrepaired chromosomal breaks or aberrant gene translocations, leading to loss or scrambling of the genome, and consequently, susceptibility to cancer.

Recently, Dr West's laboratory has focused on the breast cancer predisposition genes *BRCA1* and *BRCA2*, whose encoded proteins function in both DSBR and HR. Approximately 20% of breast cancers are heritable, with one third of these linked to *BRCA1/2* mutation. One defective copy of *BRCA1/2* in the genome is sufficient to confer cancer predisposition; the loss of the second allele is commonly observed in tumours from predisposed individuals. Of the approximately 80,000 predisposed individuals in the UK, more than 70% will develop breast cancer. Biochemical studies investigating components of the DSBR cancer-suppression pathway are therefore extremely important.

The RAD51 protein is a key player in recombinational repair, catalysing the specific reactions required for DNA pairing and strand exchange. It localises to nuclear 'foci', spots where repair reactions are thought to take place. Localisation of RAD51 is dependent upon the tumour suppressor BRCA2 (2), with which RAD51 interacts via six of eight degenerate motifs called BRC repeats (3). BRCA2 is thought to be a universal regulator of RAD51-like recombinase activity.

A recent paper from the West laboratory details the first-time purification and characterisation of full-length BRCA2 (4). The full-length protein was found to bind selectively to single-stranded DNA structures commonly seen during HR and DSBR. In addition, BRCA2 could direct the binding of RAD51 at these sites and stimulate RAD51-mediated DNA strand exchange, providing direct molecular evidence for the role of BRCA2 in the suppression of genome instability.



Damage control. DSBR occurs during the S and G2 phases of the cell cycle, when chromosomes have replicated but not yet divided (Image courtesy of Wellcome Trust Images).

This review has presented just one of the research themes in Dr West's laboratory. His talk later this term is sure to be enlightening for both those interested in the basic mechanisms of DNA repair and recombination, as well as researchers interested in the wider context of cancer biology.

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A novel strategy for inducing enhanced mucosal HIV-1 antibody responses in an anti-inflammatory environment

Wegmann F, Krashias G, Lühn K, Laamanen K, Vieira S, Jeffs SA, Shattock RJ, Sattentau QJ (2011) *PLoS One* **6(1):e15861.**

HIV-induced Acquired Immunodeficiency Syndrome (AIDS) is one of the world's greatest pandemics. Vaccine development, based on the induction of mucosal immunity, has been hampered by the low immunogenicity of HIV-1 envelope glycoproteins (Env) and the absence of mucosal adjuvants. Therefore, efforts are focusing on identifying compounds that increase Env antigenicity at the genital mucous membranes. The anionic polymer PRO 2000 interacts with the gp120 Env protein, where it masks highly variable and inaccessible epitopes. Based on this, Wegmann *et al.* tested whether the interaction between PRO 2000 and gp140 Env protein could enhance gp140 antigenicity by redirecting the immmune responses to more conserved and available epitopes.

Mice and rabbits intravaginally immunised with trimeric forms of gp140, with or without 1% PRO 2000, generated different vaginal Env-specific IgA and IgG levels. Specifically, the mice group immunised with PRO 2000 showed 5-fold higher IgA levels compared with mice without PRO 2000, while only a slight IgG increase was observed. Immunising rabbits with PRO 2000 did not result in significant increase in IgA levels, but IgG levels were increased.

Furthermore, a Th2-biased response was observed in mice boosted with PRO 2000. PRO 2000 might counteract a standard vaginal Th1 environment, generated by local bacteria, by interfering with TLR4 signalling. Surface plasmon resonance (SPR) showed PRO 2000 bound to the TLR4-MD-2 complex and blocked LPS-binding to the receptor. As, in contrast to Th1 cytokines, Th2 cytokines have an anti-inflammatory action, PRO 2000 prevents inflammation-mediated recruitment of HIV-1 target cells and thus, might help decrease HIV-1 transmission.

Western blot analysis revealed decreased gp140 proteolytic cleavage upon PRO 2000 incubation, suggesting increased antigen lifetime in mucosal regions. Indeed, among other sites, SPR and antibody binding inhibition experiments showed PRO 2000 binding to the positively charged V3 loop of gp140, which is often targeted by proteases.

In conclusion, the immune modulatory and anti-inflammatory properties of PRO 2000 reveal its potential as a vaccine formulation agent to combat HIV-1.

Molecular and structural basis of ESCRT-III recruitment to membranes during archaeal cell division

Samson RY, Obita T, Hodgson B, Shaw MK, Chong PL, Williams RL, Bell SD (2011) *Mol Cell* **41(2):186-196.**

Archaea from the genus *Sulfolobus*, such as *S. acidocaldarius*, divide by binary fission. However, they lack homologues of the tubulin and actin cytoskeletal proteins. Cell division was previously shown to be mediated by homologues of the ESCRT-III and Vps4 system, which play a role in membrane modelling processes in eukaryotes. Samson *et al.* address the question of how the ESCRT system is positioned at mid-cell during archaeal cell division, since archaea lack homologues of eukaryotic ESCRT-III positioning factors.

In *Sulfolobus spp.*, the gene coding for CdvA is located upstream of the ESCRT-III and Vps4 encoding genes. Pulldown and yeast-two-hybrid assays revealed interactions between CdvA and the winged-helix (wH)-like C-terminal domain of ESCRT-III. Overexpression of this ESCRT-III domain led to the generation of nucleoid-free cells, indicating a cell division impairment. The crystal structure of a fragment (the E3B peptide) of CdvA interacting with ESCRT-III suggested that CdvA bound by inserting a β strand between two β strands of ESCRT-III, forming a novel winged-helix-like architecture.

CdvA was localised at mid-cell between divided nucleoids, with the CdvA structures shrinking as the membrane constricted during cell division. CdvA structures were also found in cells with non-segregated nucleoids, and perpendicular to the division plane. Since transcript analyses have indicated that CdvA is expressed before ESCRT-III, CdvA may form structures prior to ESCRT-III, followed by ESCRT-III recruitment. Indeed, liposome-binding assays revealed CdvA binding to liposomes, and recruitment of ESCRT-III. Moreover, electron microscopy analysis showed extensive liposome deformation upon incubation with both proteins.

These results demonstrate the fundamental role of CdvA in positioning the archaeal ESCRT machinery during cell division.

ENLIGHTENMENT

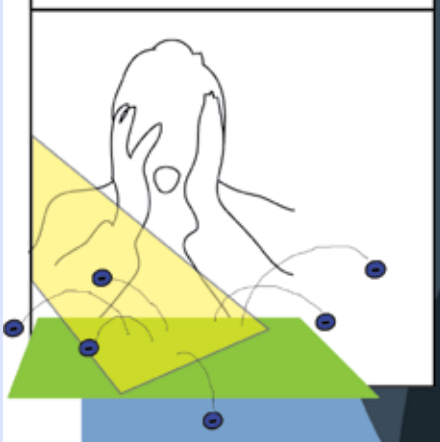
Stranks SD, Weisspfennig C, Parkinson P, Johnston MB, Herz LM and Nicholas RJ (2011) Ultrafast charge separation at a polymer-single-walled carbon nanotube molecular junction. Nano Lett 11(1): 66-72

Oil is running low, unstable politics threaten supplies, and the greenhouse effect messes with the weather; wouldn't it be nice if there was an alternative energy resource?

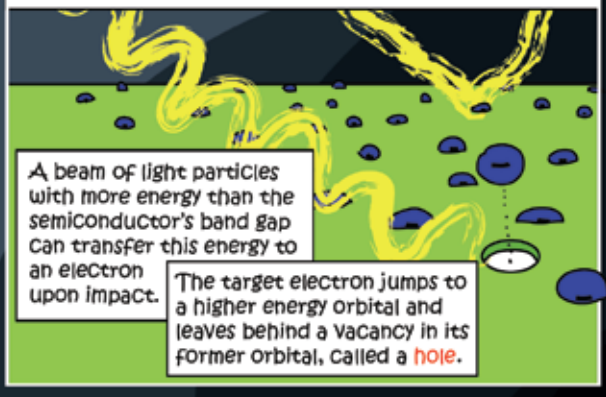
There is!

Every hour the sun supplies enough energy to Earth's surface to cover our entire annual energy consumption, so harvesting solar energy is a bright idea.

Solar energy arrives in the form of electromagnetic beams. In 1887, Heinrich Hertz discovered that if he shone light on some materials, they ejected electrons. Hertz called this the photoelectric effect.



Today, we know that a material's atomic orbital-setup determines how much energy is needed to unbolt an electron. In conductors, peripheral electrons are already loose and shared between nuclei. Semiconductor nuclei are more possessive and require a particular energy, called the band gap, to loosen an electron.



A beam of light particles with more energy than the semiconductor's band gap can transfer this energy to an electron upon impact.

The target electron jumps to a higher energy orbital and leaves behind a vacancy in its former orbital, called a hole.

Solar cells are all about rapidly luring that electron away from its hole. If you can bias the electrons' route, you've got electricity.

Indirectly, holes travel too: if the hole is replenished by another electron, that electron must have arrived after leaving another hole.

In effect, the hole has moved.

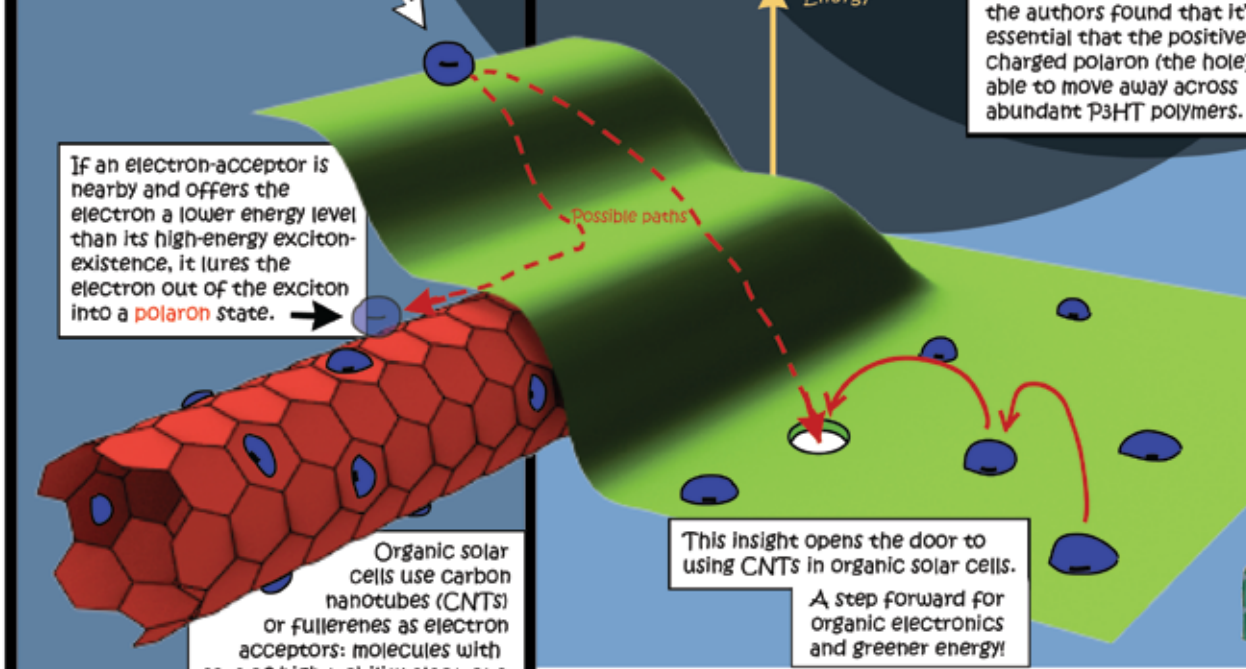
First-generation solar cells use silicon, which has a small band gap, so that even low-energy sunbeams can liberate electrons. Silicon solar cells are efficient but fragile, inflexible and expensive.

So, researchers have come up with alternative photoelectric materials.

Organic solar cells use long conjugated organic molecules with a large band gap, such as poly(3-hexylthiophene), P3HT, to absorb light. The excited electron and its hole remain electrostatically bound as an exciton.

Recently, Oxford researchers studied P3HT to CNT electron transfer kinetics with unprecedented time resolution, and found that electron transfer occurs in just 450 femtoseconds.

However, oppositely charged polarons can recombine, and the authors found that it's essential that the positively charged polaron (the hole) is able to move away across abundant P3HT polymers.



If an electron-acceptor is nearby and offers the electron a lower energy level than its high-energy exciton-existence, it lures the electron out of the exciton into a polaron state.

Organic solar cells use carbon nanotubes (CNTs) or fullerenes as electron acceptors: molecules with seas of high mobility electrons.

This insight opens the door to using CNTs in organic solar cells.

A step forward for organic electronics and greener energy!

by Caroline Dean in conversation with Dr Laura Herz and featuring Gabriel Villar on Lightwave

Anterior patterning during mammalian embryogenesis

Dr Shankar Srinivas

Embryonic development does not simply consist of a preformed miniature foetus or 'homunculus' growing in size. It is a tremendously dynamic process, characterised by a great deal of cell movement and tissue rearrangement. For example, during embryogenesis the forming heart starts in front of the forming brain, and only comes to lie in its more familiar position with respect to the brain following extensive tissue movements.

An understanding of development is important on many levels. It is medically important, directly because it can help us understand congenital abnormalities, and indirectly as many of the basic developmental processes, like cell differentiation and migration, play major roles in the body long after birth both in normal and pathological situations. Intellectually, it is also an intriguing process. Information stored in our genome is reliably converted into the shape of our body through an exquisitely choreographed series of events, a good understanding of which still eludes us.

An embryo starts as a single fertilised egg that divides to form a mass of cells. Over the course of embryogenesis a pattern, in the form of different types of tissue, emerges from this initially inchoate collection of cells. This complex process requires strict control.

Anterior patterning

Anterior patterning, which takes place shortly after implantation in mammals, is the process by which the head end of the body is properly specified and positioned. At this stage, mouse embryo tissue is arranged in a cylinder composed of two layers and is referred to as the 'egg cylinder'. The inner layer is made up of two types of tissue, the epiblast and the extraembryonic ectoderm (ExE). The outer layer is the visceral endoderm (VE), a simple epithelium with a critical developmental role (Figure 1). Though the foetus is derived predominantly from the epiblast, it is the cells of the VE that are responsible for specifying anterior patterning in the epiblast.

The anterior visceral endoderm (AVE), a signalling centre within the VE, is responsible for the correct orientation of the anterior-posterior axis in the mouse embryo (1, 2). The AVE is induced at the distal tip of the egg-cylinder in response to signals from the epiblast. Nodal, a member of the transforming growth factor beta (TGFß) family of proteins, is expressed in the epiblast and is required for AVE formation (3).

From their initial position at the distal tip of the egg cylinder, AVE cells migrate 'upwards' before coming to an abrupt stop at the junction between the epiblast and ExE, approximately midway up the egg cylinder (4) (Figure 1). From this location, the AVE induces anterior pattern in the region of epiblast closest to it and restricts the expression of posterior markers to the region farthest from it (1, 5), causing the anterior-posterior axis to be orientated orthogonal to the proximal-distal axis of the egg cylinder. Failure of AVE migration is seen in various mutants and leads

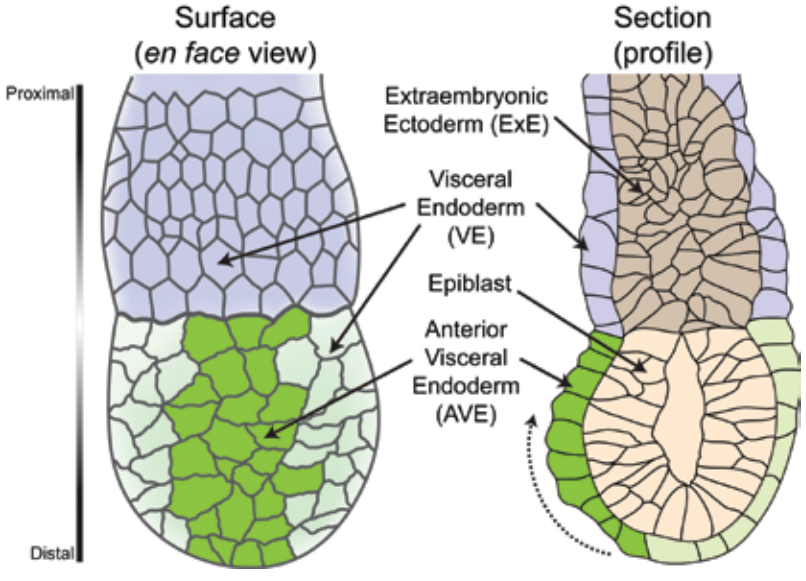


Figure 1. Diagram of a post-implantation mouse embryo showing the AVE at its anterior location. The VE is an epithelial sheet that covers both the epiblast and ExE. The AVE (green) is a subset of cells in the VE responsible for specifying anterior pattern. They are initially positioned at the distal tip of the egg cylinder, but migrate proximally, thereby orientating the anterior-posterior axis of the foetus orthogonally to the proximal-distal axis. The dotted arrow shows the path the AVE cells would have taken when migrating from the distal tip.

to faults in the pattern of the epiblast, resulting in a non-viable embryo.

Time-lapse microscopy of embryos expressing a green fluorescent protein that marks AVE cells shows that they actively migrate over a period of four to five hours and are extremely dynamic. Once AVE cells reach the border of the ExE, they abruptly cease moving proximally and start moving laterally along the boundary, as if following a barrier to the migration path (4, 6). Recent reports have shown that the VE remains an intact epithelial layer during AVE migration (6, 7). The tight and adherens junction markers, ZO-1 and E-cadherin, are present continuously along all cell borders of the entire VE during migration (Figure 2). The VE remains a monolayer during AVE migration, suggesting that AVE cells migrate between the surrounding VE cells rather than on top of them. Thus, it seems necessary for AVE cells to negotiate their way through the VE without breaking epithelial integrity.

Since generally only AVE cells are visualised, very little is known about how surrounding VE cells respond to, or influence, AVE migration. For example, it was unknown if the cells surrounding AVE cells are motile and whether VE cells 'ahead' of the migrating AVE are displaced onto the ExE, displaced laterally or removed in some other way, for instance through cell death. Why AVE cells stop moving proximally upon reaching the ExE was also unknown, particularly given that the VE overlying the epiblast and ExE are part of a single continuous sheet.

We have recently addressed some of these questions using time-lapse microscopy to record the behaviour of all VE cells (both AVE and non-AVE). We have shown that VE cells overlaying the epiblast shuffle around during AVE migration, exchanging positions in a coordinated manner with other VE and AVE cells, leading to the directional migration of AVE cells (7). Moreover, like AVE cells, those VE cells just 'ahead' of the AVE are also unable to move beyond the boundary with the ExE (magenta cells in Figure 3). Interestingly, VE cells overlying the ExE show dramatically different behaviour compared with VE cells overlying the epiblast. They are relatively regular in shape and do not move around much or swap positions with neighbouring cells (7). Thus, the barrier to AVE migration appears to be due to regional differences in cell behaviour, caused by a region of VE that is resistant to the cell rearrangement required for AVE migration.

The molecular control of AVE migration

The molecular basis for AVE migration remains unclear. It has been suggested that AVE cells migrate in response to an external diffusible signal. One candidate for this signal is the secreted protein dickkopf (Dkk1), which is expressed just ahead of migrating AVE cells and acts as a guidance cue for the AVE (8). Dkk1 inhibits the Wnt family of proteins (named after the fruit-fly gene *wingless*) that are important in many patterning and morphogenetic processes during embryogenesis. Specific Wnt proteins transmit signal via distinct intracellular signalling cascades, the best understood being the 'canonical' pathway. Dkk1 is thought to guide AVE cells by inhibiting the canonical Wnt pathway. However, evidence has emerged suggesting the involvement of another branch of the Wnt signalling pathway in AVE migration, called the Planar Cell Polarity (PCP) pathway.

PCP signalling is responsible for coordinating morphogenetic events across fields of cells, such as the regular orientation of bristles on a fly's wing, or the coordinated movement of cells towards the midline during embryonic axis elongation (9, 10). Dishevelled (Dvl) is a key mediator of Wnt signalling through both canonical and PCP pathways. Dvl translocation to the cell membrane from the cytoplasm is a hallmark of PCP signalling. We have found that the two behaviourally distinct regions of the VE show dramatic differences in dishevelled-2 (Dvl2) localisation. Dvl2 is membrane-localised specifically in the VE overlying the epiblast, suggesting there is active PCP signalling in this region of robust cell movement. In contrast, Dvl2 is excluded from the plasma membrane in the behaviourally static region where the VE overlies the ExE. Genetically perturbing PCP signalling also perturbs AVE migration, further strengthening the notion of a link between the two (7).

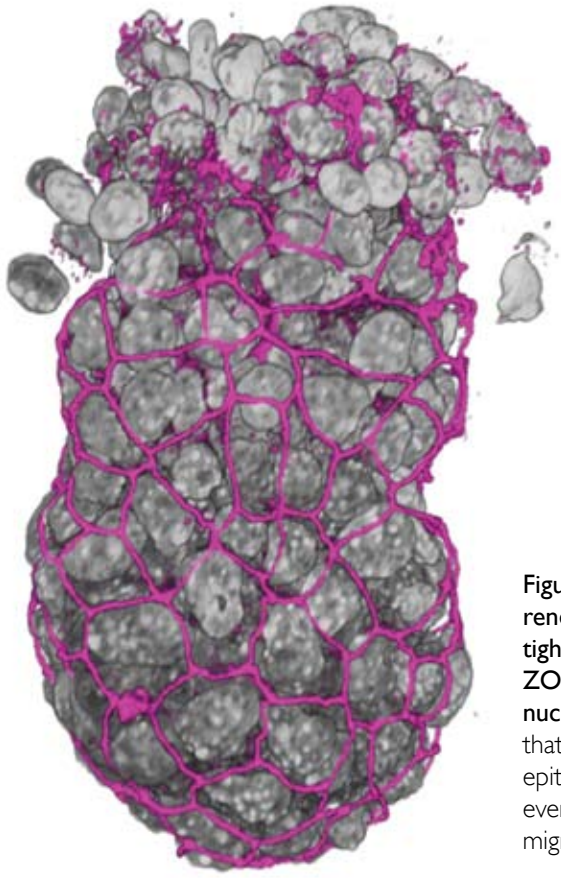


Figure 2. Volume rendering of the tight junction marker ZO-1 (magenta) and nuclei (grey) showing that the VE retains epithelial integrity even during AVE migration.

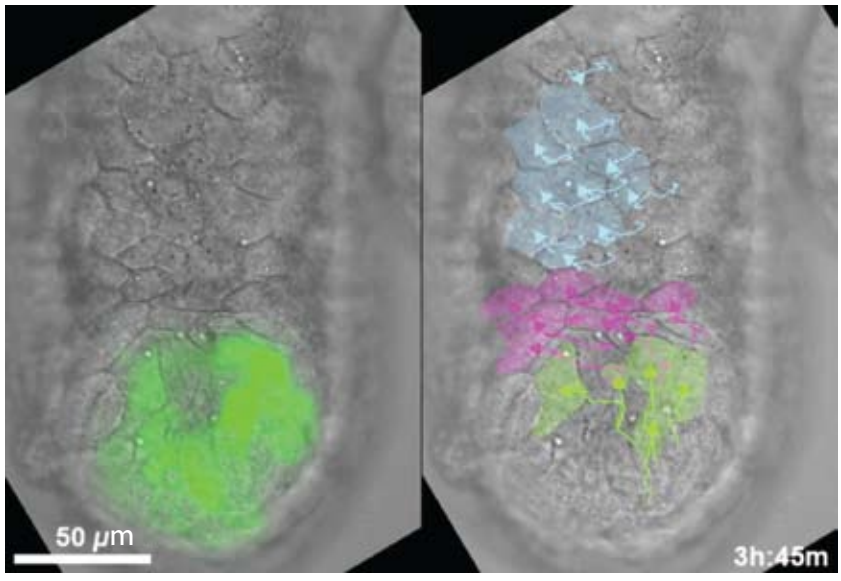


Figure 3. A single frame from a time-lapse sequence of neighbour exchange during AVE migration. The embryo is orientated with anterior towards the reader. AVE cells are marked by GFP expression (green). The same embryo is shown in left and right panels. In the right panel, selected VE cells just 'ahead' of the AVE (magenta) and overlying the ExE (blue) are outlined to highlight differences in movement. Arrows show the tracks of moving cells.

One of the primary ways in which PCP signalling influences cell movement is through the molecular motors non-muscle myosin IIA and F-actin, that together facilitate cell movements within epithelia (11, 12). Mutants of Nap1, a regulator of actin branching, have AVE migration defects (13). The small GTPase Rac1 modulates cytoskeletal dynamics in response to PCP signals. Recently it has also been demonstrated that Rac1 mutants have AVE migration defects (6). The two behaviourally distinct regions of the VE also show dramatic differences in the localisation of F-actin and myosin IIA (7).

How are these signals that regulate the morphogenetic process during anterior patterning coordinated with the signals that regulate cell differentiation? We are starting to get a hint of how this might be achieved from experiments that show that Nodal is also required for the VE PCP signalling that modulates AVE movement (7). Nodal mutants show a disruption of membrane Dvl2 localisation. In a complementary manner, mutants for a secreted inhibitor of Nodal called Lefty1 show ectopic membrane localisation of Dvl2.

Although our understanding of AVE migration is still imperfect, these findings provide tantalising insights into possible mechanisms by which PCP signals might demarcate regions of differing behaviour within epithelia, thereby regulating the cell movements that go on to shape the embryo.

Dr Shankar Srinivas is a University Lecturer in the Department of Physiology, Anatomy and Genetics, University of Oxford.

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GRASS TO GAS

Dr Sarah McKim

Keeping people and goods moving is the single most energy-demanding process in the UK. In 2009, transport accounted for approximately 40% of the total energy consumed, almost all from fossil fuels (1). Finite supply and political concerns associated with fossil fuels have driven interest in possible replacement energy sources for decades. However, the rapid warming of our climate due to greenhouse gases, such as carbon dioxide, emitted from burning fossil fuels has provided a pressing incentive to find alternative transport fuels with significantly lower carbon dioxide emissions.

Biofuels rather than fossil fuels

Harnessing the vast amount of solar energy constantly hitting the earth's surface may be part of the answer to a carbon-sustainable, post-fossil fuel world. Of the solar conversion technologies available, none match the efficiency of photosynthesis carried out in plants and microorganisms (2). During photosynthesis, energy from sunlight is used to split water and fix carbon dioxide into energy-rich carbohydrates, used by the organism to accumulate biomass. The past few years have seen great interest in transforming biomass into liquid transport fuels such as ethanol and butanol, the so-called 'biofuels'. In many countries, bio-ethanol fuels are already in use; for instance, all automotive fuel sold in Brazil contains at least one-quarter sugarcane ethanol.

Fossil fuels themselves also derive from biomass, but from organisms which lived during the carboniferous period (~280-350 million years ago). Intense geological pressures and temperatures transformed this decaying matter into energy-dense fuels such as coal, petroleum and natural gas. Burning these fuels over the last century released massive quantities of carbon dioxide, originally fixed over hundreds of millions of years, leading to an increase in carbon dioxide in our atmosphere. Modern-day biofuels forgo this substantial period between carbon dioxide fixation and release. Since the carbon dioxide produced during the combustion of biofuels was only recently removed from the atmosphere, the net carbon dioxide emission is theoretically much lower than that from fossil fuels (Figure 1).

Figure 1. Carbon cycling. Carbon released from biofuel was recently captured from the atmosphere (arrow) in contrast to carbon derived from fossil fuels.

Biofuels are an especially attractive replacement transport fuel as they can fit easily into the existing transportation infrastructure. Although they may seem new, biofuels have long been associated with transport. In fact, Henry Ford's Model T car was designed to run on petrol, ethanol or both. However, despite the costs associated with extraction and refining, the sheer volume of very high energy density fossil fuels made them more competitive than other fuel options. Even with the much higher prices of today, fossil fuels still account for 86% of global energy consumption (3). Moreover, increasing prices have the knock-on effect of making previously uneconomic sources, like tar sands, financially viable thus prolonging our dependence on fossil fuels.

Why are we not using biofuels already?

A significant obstacle to rendering biofuels economically feasible is the high cost of both growing plant biomass and its bioconversion into fuel. Biofuels currently available, like bioethanol, are produced by fermentation of the starch and sugars found in food crops such as maize and sugarcane. Domesticated crops are incredibly productive compared to their wild progenitors. However, thousands of years of breeding has selected for traits favourable to food stuffs and storage rather than biofuel production.

Another important issue associated with biofuels is land use. According to the Food and Agriculture Organisation of the UN, close to one billion people on earth are undernourished. This raises ethical concerns when land which could be used to grow food is diverted towards biofuel production. Recent research also suggests that growing food crops for energy rather than food is a less productive use of the land due to inefficiencies in the bioconversion process (4). Moreover, carbon dioxide released from energy consumed in farming and refining biomass has implications on the actual carbon sustainability of biofuels. To help combat these difficulties vigorous research is being conducted on a global scale to develop non-food 'energy crops' with increased productivity, bioconversion efficiency and carbon sustainability while addressing the need to preserve land for food production.

Non-food energy crops may provide an answer

Two non-food energy crops receiving intense attention are miscanthus, usually the hybrid *Miscanthus x giganteus*, a temperate grass from Southeast Asia, and switchgrass, *Panicum virgatum*, a North American temperate grass. These species are fast-growing and generate lots of biomass each season (Figure 2). As perennial grasses, they die back at the end of the growing season and mobilise nutrients from leaves and stems into the roots to have ready for the next year. Thus, harvesting the above-ground parts of the plants after the growing season leaves nutrients in the soil, leading to a decreased need for fertiliser. Additionally, grasses like miscanthus and switchgrass have specialised leaf anatomy permitting C4 photosynthesis. This is a more efficient carbon fixation process than the standard C3 photosynthesis, allowing C4 plants to grow on nutrient-poor soils and withstand stresses, especially drought, better than other plants (5). These characteristics highlight an important feature of using energy grasses as biofuels; ideally these crops would be grown on what would otherwise be marginal agricultural land, thus not diverting as much land from food production.

Many other species are contenders to become energy crops, such as reed canary grass, Napier grass and agave. Plant biologists are exploring natural variation within C4 grasses to identify the best varieties to become energy crops. For instance, a team at Rothamsted Research in the UK is investigating how to breed improved strains of native coppice willow (6). Choosing region-specific energy crops has the additional benefit of supporting a model where biofuels are produced locally, reducing both the cost and carbon footprint involved in transport from growth in the field to bioconversion and combustion.

Figure 2. The energy crop *Miscanthus x giganteus*

The biofuel utility of a non-food crop is dependent on converting its inedible biomass into biofuel. While current biofuels utilise the edible sugar and starch containing parts of the food crop, biofuels in development aim to unlock the potential of cellulose. The most abundant organic compound on earth, cellulose is a polysaccharide forming the major structural component of plant cell walls and is inedible for humans. Cellulose is made up of chains of hexoses arranged into microfibrils which are linked together by hemicellulose, a pentose- and hexose- based polysaccharide. In the primary cell wall, this lattice is embedded within a pectin matrix while in the much thicker secondary cell wall, cellulose and hemicellulose are often sandwiched in a mesh of lignin, a complex phenolic polymer which adds strength, water impermeability and a measure of pathogen resistance (Figure 3).

Up to 50-60% of crop biomass is comprised of these lignocellulosic cell wall components. Extracting and

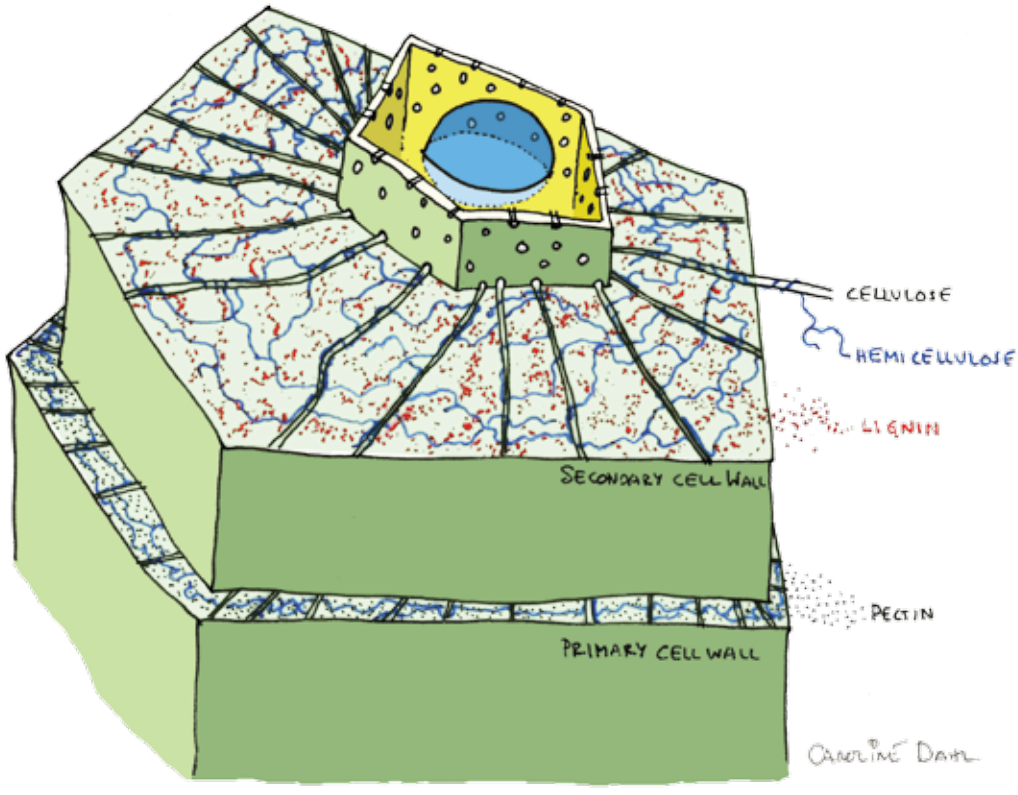

Figure 3. The plant cell wall. All growing plant cells are surrounded by a primary cell wall outside the plasma membrane. Some cells develop a thicker, secondary cell wall between the primary cell wall and plasma membrane after they stop growing. This secondary cell wall is stronger due to the presence of lignin, a complex phenolic polymer which lends rigidity, water impermeability and resistance to pathogens.

fermenting sugars contained within the cell wall to generate ethanol or butanol will vastly increase the productivity of biofuels. Unsurprisingly however, plant cell walls are resistant to degradation. Current technologies to liberate sugars from the cell wall include enzymatic hydrolysis of cellulose, a costly process due to the quantity of enzyme required, and degradation of hemicellulose through acid treatment in conjunction with elevated temperature and pressure. Unfortunately, the efficiency of all these steps is severely impaired by the presence of lignin.

Improving the efficiency of biomass to biofuel conversion

Research is ongoing to improve the efficiency of converting cell wall polysaccharides into sugars and in particular, to mitigate the inhibitory effect of lignin on cellulose availability and bioconversion (7). One approach is to decrease the amount or alter the structure of lignin within the cell walls of the energy crop. A recent publication by Fu *et al.* describes the development of a genetically modified switchgrass containing lower amounts of lignin and altered structural characteristics which led to a 38% increase in ethanol yields following fermentation (8). Importantly, Fu and colleagues showed that less severe pre-treatment and a smaller dose of enzymes was required to liberate cellulose. Moreover, these transgenic lines did not show massive phenotypic differences compared with native switchgrass, regardless of altered lignin composition. It remains to be seen whether these plants are more susceptible to plant disease due to changes in lignin content. This work strongly suggests that transgenic modification may be a useful route to improving biofuels. This approach can be complementary to exploiting natural variation in lignin characteristics and content in prospective energy crops.

Once sugars have been extracted from lignocellulosic biomass, they must be fermented to yield liquid fuels. Methods to increase the efficiency of fermentation include improving microbial conversion processes by using specially designed yeast strains. An exciting recent advance by Ha *et al.* showed genetically modified yeast which can ferment both hexoses from cellulose and pentoses from hemicellulose, in contrast to current strains used which only ferment hexoses (9).

Model genetic systems also have a role to play in biofuel development. Understanding the dynamics of cell wall formation and composition in the genetic model *Arabidopsis thaliana* has been crucial to advances in energy crop development. Knowledge of the genetic control of shoot branching, also gained from work in *Arabidopsis*, is currently being applied to develop coppice willow strains with architectures beneficial to biomass production (10). Although the utility of *Arabidopsis* is undisputed, it is an annual herbaceous species, not a grass, and thus is limited for study of certain aspects of grass biology. Recent efforts to address this problem have resulted in the development of a grass model system, *Brachypodium distachylon*, which holds promise as a model energy crop (11).

The creation of a new industry, especially with an ambitious scope such as biofuels, is an exciting process to witness. From genetic modification to natural variation through to bioengineering, research is underway to generate biofuels which can compete economically with fossil fuels. It is too early to say which avenue may provide the best return, but they may lead to biofuels powering a part of our transportation future.

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Neuro-mechanical interfaces: Using brain activity to control machines

Dr Carinne Piekema

Would you be happy to stay onboard a plane if you knew the pilot was sitting in his armchair flying it with only his thoughts? This may sound like science fiction, but the Defense Advanced Research Projects Agency (DARPA) in the USA has already spent millions of dollars on research that focuses on the interaction between the human brain and machines. Mind-controlled aeroplanes and battle robots are high on their wish list.

While armies of robots are still a distant goal, the progress made so far could have a tremendous impact on the lives of people suffering from paralysis. Often caused by diseases such as stroke or by spinal cord injury after an accident, in extreme cases paralysis can lead to locked-in syndrome. Over the past couple of decades, research into paralysis has focused on the development of a brain-machine interface (BMI) that allows people to control muscles and even prosthetic limbs through thought alone.

To understand the magnitude of this development, we have to look back in history. Wilder Penfield laid an important part of the foundation when he was working at McGill University in Canada in the 1950s. Penfield, who studied neuropathology at Merton College in Oxford, became well known for treating epilepsy patients by destroying neurons at the foci of the seizures. Before each surgery, he would electrically stimulate the brain of the conscious patient to localise brain function. This allowed him to guide his surgery more precisely and prevent damage to other cognitive and motor functions. It also enabled him to draw a complete map of the motor cortex, or motor homunculus (Figure 1). The sizes of the body parts on the cortical map correspond to the complexity of the movements that those parts perform. Our ability to perform the fine scale movements required to speak or use tools is clearly reflected in Penfield's map.

Further exploration into motor functioning led Eberhard Fetz and colleagues to discover that monkeys were able to voluntarily control neural activity through operant training when given biofeedback (1, 2). Monkeys with electrodes implanted in their brain looked at a meter showing their own neuronal activity. Whenever the meter needle pointed to the right, the monkey received a reward. As soon as the monkeys learnt that the meter reading and the reward were linked, they were able to adjust their neural firing patterns to obtain more rewards. Initially the neuronal activity still resulted in active movement of the monkeys' limbs, but over time, while the monkeys still voluntarily controlled the neuronal activity, the overt movements were extinguished.

In the early 1980s, researchers discovered that ensembles of neurons found across the brain create particular movements (3). Until then it was thought that only a few certain neurons were responsible for each specific movement. Looking for an ensemble instead of a few particular neurons amongst the 100 billion human brain cells made finding the target areas a lot easier.

By using different imaging techniques to look at widespread brain activity, Jeannerod and colleagues made an interesting discovery (4, 5). They imaged brain activity while patients imagined making a specific movement and compared these activations with that observed when the participants were actually making the movement. A striking resemblance was found between the observed activations, suggesting that imagining a movement may not be so neurally different from actually performing the movement.

In parallel, Nicolelis and Chapin trained rats to receive rewards for activating neurons in their brain normally activated by a specific movement, without making the movement (6). The rats were trained to press a lever when thirsty to receive water. During lever presses, the researchers recorded the patterns of activity from 46 neurons. The lever was then disconnected from the water supply, so that the rat no longer received water from a lever press. However, the rat continued to press the lever when it was thirsty and now received water whenever its brain produced the command for pressing the lever. After a while, the rat stopped pressing the lever altogether, but kept producing the 'press lever' command in its brain. The external machine that delivered the reward was directly operated through the 'press lever' command in the rat's brain.

In a further study that extended to primates, Nicolelis and his colleagues taught monkeys to swing an artificial arm from left to right by thought alone, using a similar method to that outlined above (7). To attempt more complex movements, the monkeys were taught to use a joystick to drag a cursor onto a target on a computer screen while the researchers recorded

the patterns of brain activity as before. Soon, the monkeys learned that the command for 'drag cursor' alone resulted in a reward, and they stopped actively dragging the cursor onto the target. Commands for 'reach' and 'grab' were implemented in a similar way.

Through this research, scientists are now able to create communication pathways between the brain and an external machine: the computer cursor or an artificial limb. The first human trials have successfully shown that paralysed patients are able to directly control computer cursors (8). However, they have also raised issues that need to be addressed about the safety and reliability of the intracranial electrodes used before clinical trials can be extended to larger patient populations.

Another limitation of current-generation BMIs is a lack of sensory control. To successfully sip from a cup of tea requires more than just reaching and grabbing movements. The touch sensors that send signals from our hand to our brain allow us to pick up the cup without knocking it over. However, an artificial extremity has no such sensors. Thus, we need feedback of information from the external device to the brain. The only feedback currently available is visual feedback, which gives insufficient control over artificial limbs. A recent article in the *Journal of Neuroscience* showed that adding sensory feedback information would greatly increase control (9).

Research is also focusing on the striking finding that the brains of the monkeys that participate in these studies become structurally adapted to the external devices (10). Thus, different areas within the motor cortex of these monkeys now seem to be representing the robot, as if the robot was a part of their own body. If further research proves this to be right, the implications might be unprecedented. It would allow the patient to perceive the prosthetic device as an actual part of their body.

A global team of neurophysiologists, computer scientists, engineers, roboticists, neurologists and neurosurgeons are now working together in the Walk Again Project to develop a generation of neuroprosthetic devices that can restore full-body mobility in patients with severe paralysis. Thus, while the people at DARPA dream of armies of robots, their money has been well spent on research that could mobilise the immobile in the not too distant future.

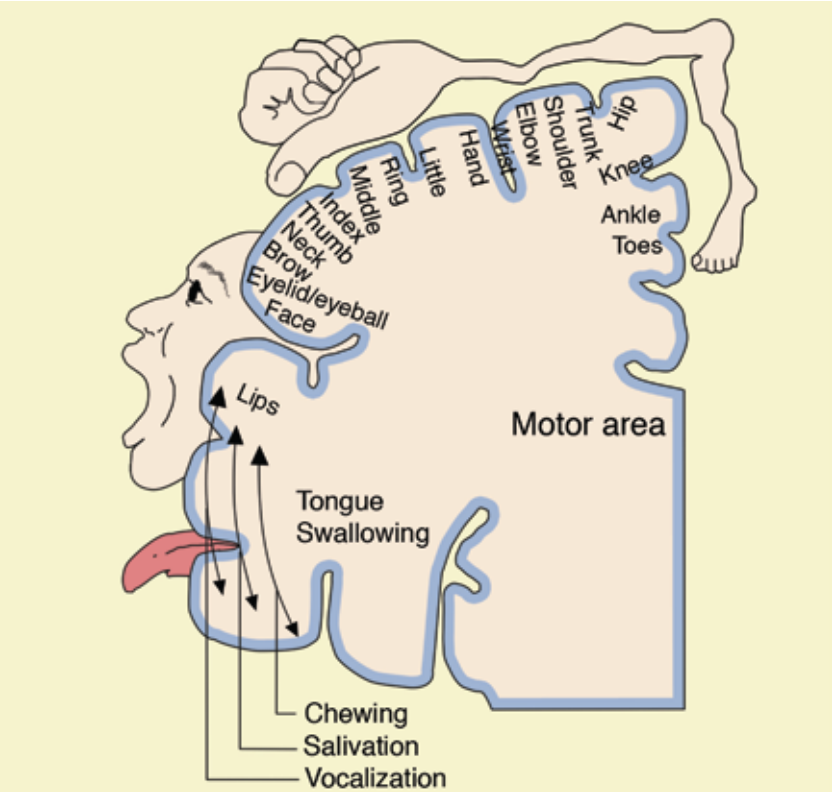

Figure 1. Penfield's cortical map.

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BUGS THAT EAT OIL

By Penny Sarchet

The explosion on the *Deepwater Horizon* oil rig in April 2010 was the most publicised environmental disaster since Chernobyl. Oil continued to spill into the Gulf of Mexico for three months, but by November, 99% of fishing areas had already reopened. The speed of recovery after a spill depends upon the oil's composition, the climate and the degree of dispersal, all of which have a large impact upon the ability of a group of naturally occurring microbes to 'eat' this oil.

An Ecological Niche

Every year, hundreds of millions of litres of oil leak into the environment from a combination of human and natural sources. Crude oil forms in underground reservoirs, trapped by layers of rock. These oil basins can typically be leaky due to pressure build-up or tectonic movements. As a consequence, sudden releases of petroleum into the surrounding environment have occurred naturally since long before humans began to tap and transport it as fuel. It is estimated that natural marine oil seeps alone leak enough every year to cover the planet's oceans with a layer of oil 20 molecules thick.

This natural release of oil provides an ecological opportunity for any organisms which can evolve to feed upon it. Bacteria that are capable of degrading leaked hydrocarbons were first isolated in 1913. In 2005 it was reported that the range of microbes that can degrade or transform hydrocarbons as part of their metabolism includes at least 79 types of bacteria, 9 types of cyanobacteria, 14 types of algae and 103 types of fungi. Research over the last 20 years has identified strains of bacteria that can use hydrocarbons almost exclusively as their only source of carbon.

Chocolate Mousse

The degree to which microorganisms can digest crude oil depends upon its composition. Crude oil is a complex blend of over 17,000 different chemicals containing four main types of hydrocarbon: alkanes, aromatics, resins and asphaltenes. Alkanes are the simplest oil chemicals and are fully saturated with hydrogen, containing no double bonds. Along with aromatic hydrocarbons (those which possess rings of alternating single and double bonds), alkanes form the lightest fractions of oil, while resins and asphaltenes are heavier, polar molecules. The composition of crude oil is determined by the environment in which it was formed and can be classed as light or heavy, depending on the proportions of its constituent fractions.

Before biodegradation of an oil seep can occur, the spill must first experience a degree of physical weathering to break it up and make the oil more accessible. The crude oil spilled from the *Deepwater Horizon's* Macondo Well was a light oil with low aromatic content. Combined with the warm climate of the Gulf of Mexico, this led to high rates of surface evaporation. Through evaporation and wave action, spilled oil can emulsify, changing from black slicks to a brownish, bubbly mixture referred to as 'chocolate mousse'. Oil-metabolising microflora can then use the emulsified oil as a substrate, preferentially removing aromatic and saturated hydrocarbons and increasing the proportion of polar constituents, which are harder to break down.

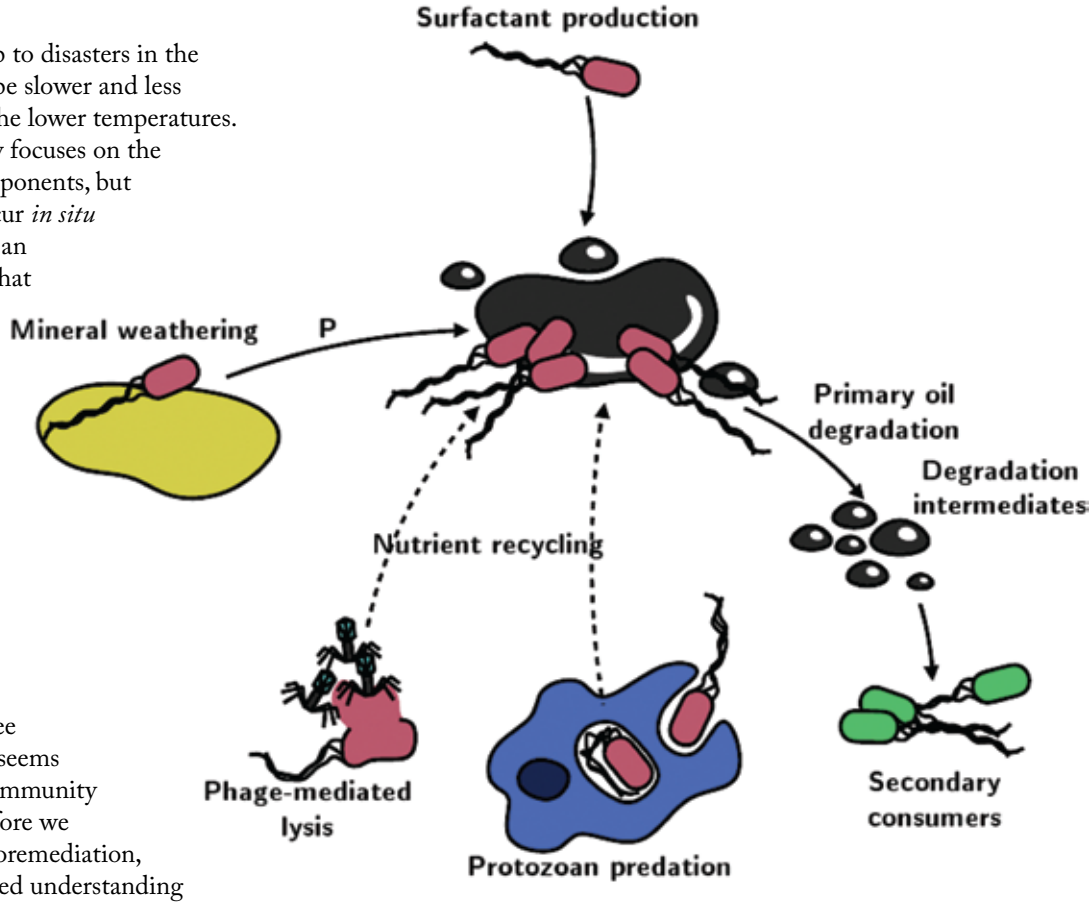
Scientists have sought to combine culture-based studies of catabolism with environmental data to determine if any species are particularly dominant in the biodegradation of oil hydrocarbons. Researchers found that bacterial *Alcanivorax* species rapidly rise in number after nutrients are added to seawater that contains oil. These species begin at undetectable levels, but after just one to two weeks, they comprise 70-90% of the prokaryotic cells present. It is thought that *Alcinavorax* may be particularly successful in competing in oil-enriched environments because it is more effective than other species at utilising branched-chain alkanes, a trait which it may have evolved in order to exploit similar molecules produced by some species of marine plankton. Other species, like those of the *Cycloclasticus* genus, are more important for the degradation of aromatic hydrocarbons. It appears that different species are capable of utilising distinct narrow groups of oil molecules as substrates for metabolism.

Using The Microbes

Though these microbes can rely almost solely on oil for their carbon intake, as living organisms they also require other nutrients to survive. Studies suggest that the natural breakdown of oil by microorganisms is most frequently limited by the availability of phosphorus and nitrogen and that fertilising oil spills with such nutrients can lead to much quicker biodegradation of the spill. This has led to the development of bioremediation techniques that add fertilisers (biostimulation) and specific strains of microbe (bioaugmentation) to oil spills in efforts to expedite their breakdown.

There are a number of difficulties, however, in

translating experiments in the lab to disasters in the ocean. Bioremediation seems to be slower and less effective at sea, probably due to the lower temperatures. Detailed research understandably focuses on the species that remove toxic oil components, but the complex interactions that occur *in situ* are far harder to examine. When an oil spill occurs, microorganisms that are capable of degrading it must compete with other organisms for nutrients, while also avoiding lysis by phages and predation by protozoa. Mutualistic interactions also appear to be significant and some laboratory studies have observed the sharing of secreted surfactants or the transfer of hydrogen between different species. So far, laboratory and field experiments have produced fairly similar findings, but there is a high degree of variability and biostimulation seems to result in different microbial community changes in every experiment. Before we can fully harness the power of bioremediation, we need to develop a more detailed understanding of the complex ecology of these important microenvironments.



The microecology of oil biodegradation. (Image by Richard Wheeler, adapted from *Nature Reviews Microbiology* 4(3):173–182).

Bioremediation Attempts

The first large-scale application of chemicals to enhance bioremediation occurred after the *Exxon Valdez* oil spill in Alaska in 1989. A certain degree of success was reported, but the affected ecosystems of the Prince William Sound were subsequently found to exhibit unusual species fluctuations. Further studies were conducted after the *Prestige* spill in 2002 off the Atlantic coast of Galicia. Here, bioaugmentation attempts were found to have little impact. However, biostimulation techniques based upon those used in the *Exxon Valdez* clean-up effort were more successful. Fertilisers were added to the site that released their nutrients slowly and were oleophilic – meaning they showed a stronger affinity for oil than water so could contribute to emulsifying the spill. Scientists compared the patterns of attenuation at two sites in order to compare the differences between natural biodegradation and stimulated bioremediation. They found that the application of fertilisers resulted in around 10-30% extra depletion of the oil, but that fertiliser effects could not persist throughout winter, thereby necessitating expensive reapplications.

In time, the *Deepwater Horizon* spill will provide further insights into how best to harness these oil-loving microbes. Previous oil spill studies have shown that biological degradation is usually limited to the top layers of a spill due to insufficient penetration of oxygen, nutrients, water and the microbes themselves to lower layers. The *Deepwater Horizon* clean-up operation has seen the first ever deepwater injection of chemical dispersants and subsequent analysis should show us the usefulness of this new technique in increasing the potential for biodegradation. Microbial ecologists and chemical oceanographers strove throughout the summer of 2010 to identify the microbial species active at the spill site and to work out what exactly they were doing. Still the subject of debate, the next few years should yield some interesting advances in the science of these microbes that feed on oil.

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Flu Fighters

Boosting your chances of beating the flu

Dr Hayley Crawford

Post-doctoral researcher at the Weatherall Institute of Molecular Medicine.

Scientists at Oxford University's Jenner Institute have developed and tested a vaccine that may protect humans from all strains of influenza A.

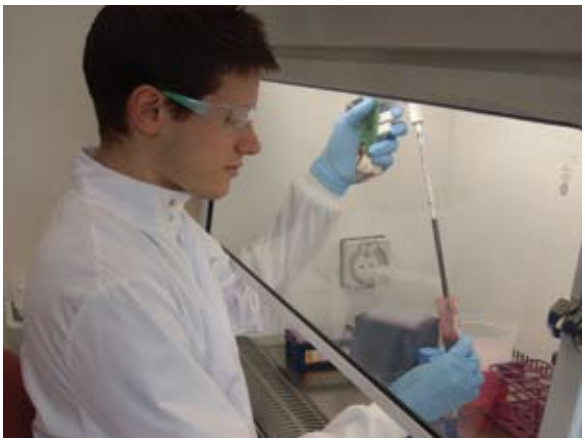
Seasonal flu epidemics affect up to one billion people each year, resulting in a quarter to half a million deaths. The 2009 'swine flu' pandemic alone killed more than 18,000 people. It was six months before a vaccine against this strain was developed and distributed, costing the UK government an estimated £1.2 billion.

Current flu vaccines induce humoral immunity by eliciting antibodies targeting haemagglutinin (HA), a viral surface glycoprotein. Flu strains are named according to variants of HA and another surface glycoprotein, neuraminidase (NA). For example, the recent swine flu outbreak was an H1N1 strain, and avian flu H5N1. As antigenic shifts in HA and NA lead to new circulating strains, annual vaccines must be designed to prime new antibodies in vaccinees. Children and the elderly constitute high-risk groups for seasonal flu, but previous exposure to similar viruses or vaccinations can confer immunity in older age groups.

A different approach

A new vaccine containing two conserved internal proteins of the H3N2 A/Panama/2007/99 strain has recently been shown to boost existing T cell responses in humans. This promising strategy relies on two factors: first, that people have encountered flu before and have memory T cells specific for the internal proteins nucleoprotein (NP) and matrix protein 1 (M1), as 90% of us do; second, that these proteins are sufficiently conserved between flu strains for the vaccine to boost these responses, which could then recognise the majority of circulating strains.

Dr Sarah Gilbert and her team at the Jenner Institute designed this MVA-NP+M1 vaccine, which delivers NP and M1 in a safe, immunogenic modified vaccinia virus Ankara (MVA) vector. In January 2011, they published the encouraging results of their Phase I trial (1): 28 healthy adults with pre-existing cellular responses to NP and M1 received one dose of the vaccine and were followed for 52 weeks. The responses, comprising mainly cytotoxic T cells, were boosted significantly by the vaccine. This is different to the antibody-raising response induced by current flu vaccines. However, the boosted responses waned after a year, suggesting that annual shots of the same vaccine will be necessary.



The new vaccine boosts T cell responses.

Protection after infection

Their next trial recruited 22 healthy volunteers. Half were vaccinated, then all challenged with the 2005 H3N2 Wisconsin strain. Fewer people in the vaccine group got flu than in the control group. Vaccinees had higher levels of activated T cells prior to infection than controls, whose T cells remained in a resting state. This small but important study shows that boosted T cell responses can offer broad protection against infection. In the elderly, who are less efficient at generating new antibody responses, the boosting of existing T cell responses may be incredibly beneficial.

Professor of Immunology at Oxford University, Sir Andrew McMichael, was lead author on a 1983 paper describing the intranasal inoculation of 63 individuals with a live unattenuated influenza A virus (2). Those with cross-reactive T cells cleared the virus. *Phenotype* asked him why it has taken 28 years after his early findings for a T cell flu vaccine to enter trials: "At that time, we didn't know how to make a vaccine that would boost this kind of response; plus the facility where we did the research closed down. Both the flu vaccine field and the pharmaceutical industry have been very focused on antibodies. Antibody vaccines that match the virus offer perfect protection."

"The potential of a T cell flu vaccine," he said, "is that it would plug the gap between a new pandemic virus appearing and the development of a new antibody vaccine for that strain, which is six to nine months. If this works, it could be stockpiled and ready for a pandemic."

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The Brilliant Light:

How the world's brightest laser could transform structural biology

By Narin Hengrung

In the 3 February issue of *Nature* this year, two letters were published detailing what may well become the seminal experiments for a new era of structural biology (1, 2). The letters announce 'proof-of-principle' of a technique that could allow scientists to image individual biological molecules at atomic resolution. "For some disciplines," says Dr Persis Drell, director of the SLAC National Accelerator Laboratory of Stanford University where the work was carried out, "this tool will be as important to the future as the microscope has been to the past." The tool she was referring to is the Linac Coherent Light Source (LCLS), the brightest X-ray laser ever produced.

Narin Hengrung is a first year DPhil student on the Wellcome Trust Structural Biology Programme, University of Oxford.

Structural biologists aim to understand how life works by finding the atomic structures of biological molecules. Structures can provide powerful functional insights. For example, Watson and Crick's discovery of the double-helical nature of DNA suggested mechanisms for both the storage of hereditary information and its replication (3). The mechanisms of molecular machines such as PcrA, a protein that can move along and unwind DNA, can be glimpsed by taking snapshots of them as they move through a reaction cycle (4). Structural information can also aid drug development; the rational design of drugs against HIV, influenza and chronic myeloid leukaemia would not have been possible without the atomic details of their targets.

The workhorse technique in this field involves firing high intensity X-rays at a crystal of the molecule being investigated. The atoms in this crystal interact with the X-rays to generate a diffraction pattern, much like pebbles thrown into water produce ripples that merge and clash. The resulting pattern is used to deduce the structure of the original molecule. Growing large enough crystals is, however, a notoriously uncertain and time-consuming process. Crystal growth conditions cannot be predicted and some proteins are impossible to crystallise. This stage constitutes a major bottleneck in structure determination.

Shorter, brighter pulses

The LCLS promises to put an end to the drudgery of crystallisation. Using the current method, large crystals are required because of the problem of radiation damage. Normal X-rays will destroy any single-molecule sample before its diffraction pattern can be recorded. Crystals, in which several billion copies of a molecule are arranged in a regular pattern, provide the signal amplification necessary to overcome this damage. However, the problem can theoretically be tackled in another way. If sufficient numbers of X-rays were concentrated into a massively intense, vanishingly short pulse, then a diffraction pattern could be generated before the molecule has a chance to fall apart. Consequently any sample, even fragile, single molecules, should be viewable. The completion of the LCLS finally gave researchers the opportunity to put this theory to the test. The light it produces is 10 billion times brighter than anything from previous X-ray sources. It can generate pulses that last only femtoseconds and can hit a sample with an astonishing 10 trillion photons of X-rays in a single pulse. Initial results with the LCLS seem to show that the theory does indeed hold.

These results, which appeared in *Nature*, are the culmination of work by two large multinational teams of researchers. One group, led by Dr Henry Chapman of the German Electron Synchrotron at the Centre for Free-Electron Laser Studies, looked at a problem that is representative of a major challenge in modern structural biology: the study of membrane proteins. Though these proteins make up 30% of the proteome and constitute the vast majority of drug targets, we have very little structural information about them. The team chose to work on photosystem I, a huge protein complex and one of the main components of the photosynthetic machinery. From crystals that were less than 2 μm across, orders of magnitude smaller than traditionally required and much easier to grow, the team were able to solve a structure of similar quality to the published crystal structure, albeit at a lower resolution. The second team, led by scientists from Uppsala University, Sweden, went one step further, obtaining the first glimpse of the structure of mimivirus from only single virus particles. Mimivirus has proved intractable for study by any other means as it cannot be crystallised and is too big for a full reconstruction by cryo-electron microscopy. Importantly, both studies showed that the data they collected were of native, intact protein. Radiation damage can be outrun.

The engineering behind the laser

The LCLS is an addition to the SLAC linear accelerator (linac) in Menlo Park, California. An overhead view of the site reveals a dead straight building that emerges from the edge of town, passes beneath the freeway and heads out into local woodland. Housed within this building, the linac is a long tube containing cylindrical electrodes that accelerate electrons

injected into it. At two miles, it is the longest linac in the world. By the time electrons reach its end, they are travelling at 99.999999995% of the speed of light.

The LCLS adds an extra half mile onto the linac. Its heart is a component known as the 'wiggler'. By means of a periodic lattice of magnets, it forces electrons from the linac to oscillate at a very high frequency as they travel along its length. The oscillating electrons give off X-rays and both travel together through the laser. During this journey, the electrons and X-rays interact to synchronise both the movement of the electrons and the X-rays themselves. This massively increases the intensity of the resulting beam. Getting this process right is the trickiest part of producing this type of laser as it is governed by a positive feedback mechanism. Imagine placing a microphone right next to the speakers it feeds. Just as this setup would uncontrollably amplify background noise into horrendous screeching, even tiny departures from the ideal parameters of the beam would snowball and destroy the output. For example, the beam must not deviate by more than 5 μm over its entire 130 m length (5). It is astounding that the laser works at all.

The future for LCLS studies

This doesn't mean that further work is not necessary. Though compelling as 'proof-of-principle' experiments, the two studies described have weaknesses. One issue is resolution. Often the most valuable conclusions depend upon knowing the precise positioning of key residues within a protein. Neither of these studies has reached this level of detail. In the case of mimivirus, only the overall shape of the virus particle could be seen. Resolving greater detail from single particles will require still more intense, shorter pulses of lower-wavelength photons as well as improved detectors. Sample delivery into the path of the laser also needs improvement.

If scientists manage to increase the viewable resolution for single particles, then not only will the pace of structural biology accelerate, but entirely new questions will become accessible. Without the need for crystals, the movement of proteins could be viewed in real time, allowing researchers to directly view their mechanism of action. Biologists would effectively have a strobe light for proteins. The high resolution imaging of living cells also becomes possible, potentially offering even greater detail than can be obtained by electron microscopy. With Japan and Europe already building their own LCLS-like lasers from scratch, the science is gaining momentum.

Commenting on the first successful test of the LCLS, Director of Construction Prof John Galayda said, "We were all dumbfounded. We were standing there dumbfounded, looking at the light." If the LCLS lives up to its potential, structural biologists can look forward to experiencing many more such moments themselves; gazing in awe as this light unveils the beauty of the tiniest things.

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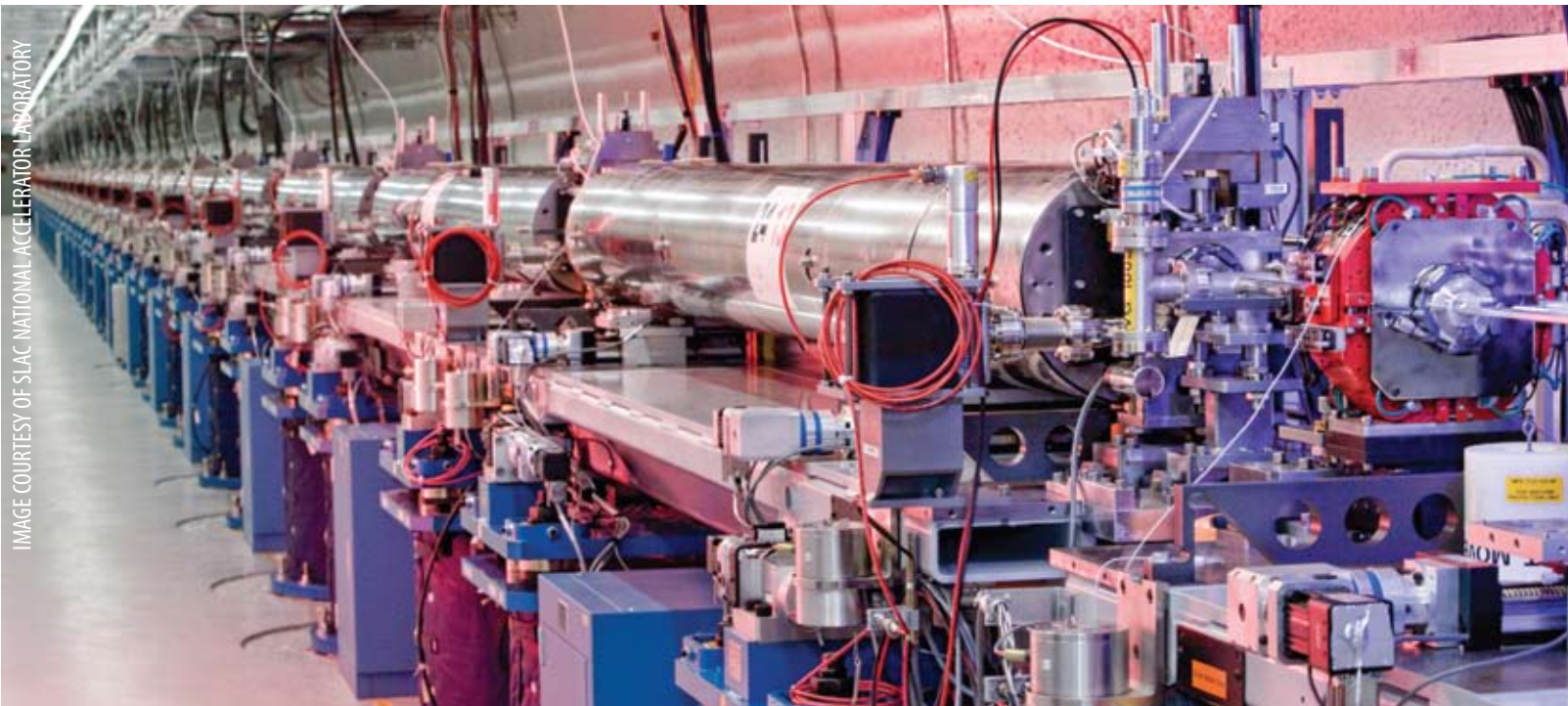
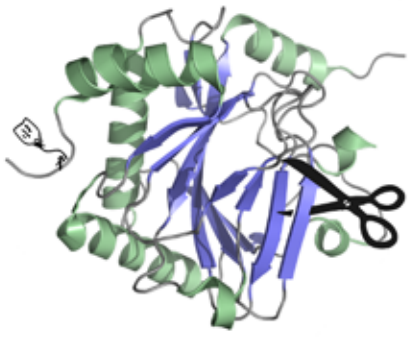
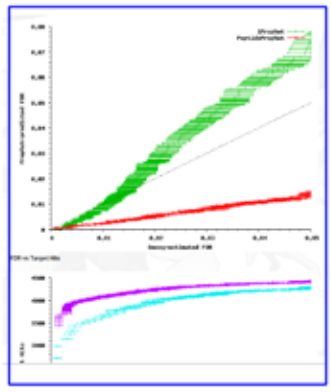
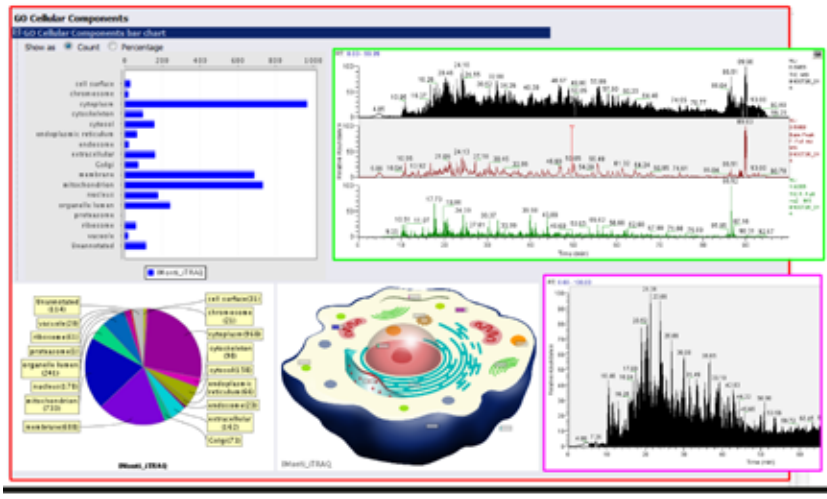


IMAGE COURTESY OF SLAC NATIONAL ACCELERATOR LABORATORY

Oxford Central Proteomics Facility







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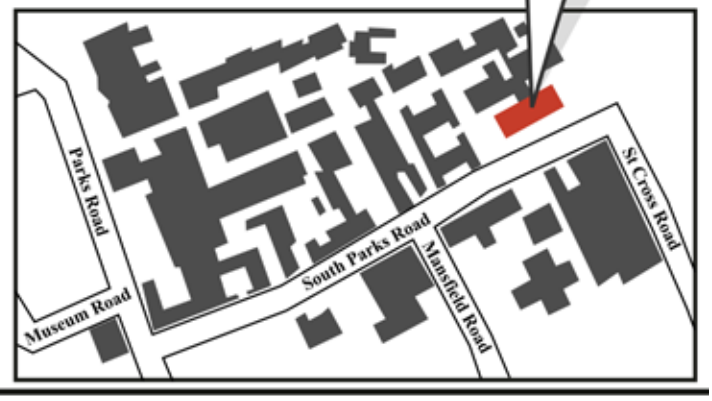

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Software Available

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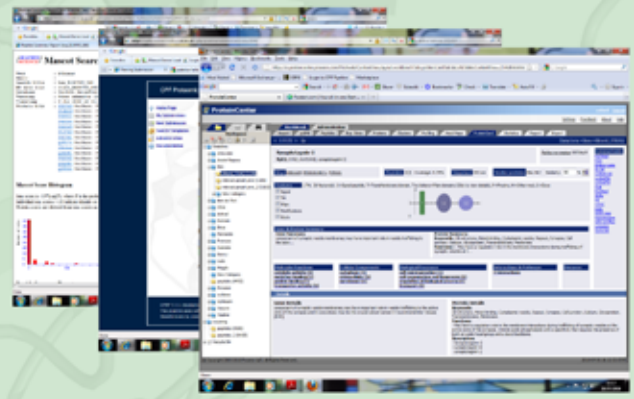
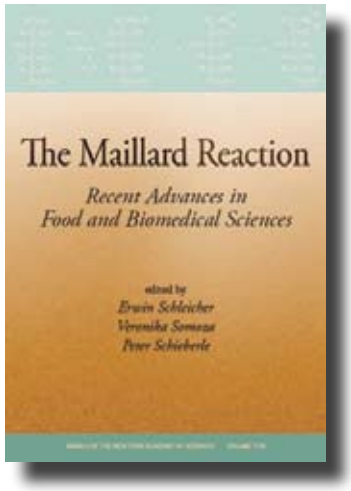


The Maillard Reaction: Recent Advances in Food and Biomedical Sciences

Edited by Erwin Schleicher, Veronika Somoza, Peter Schieberle
Wiley-Blackwell, 2010
(Reviewed by Leo Kong)



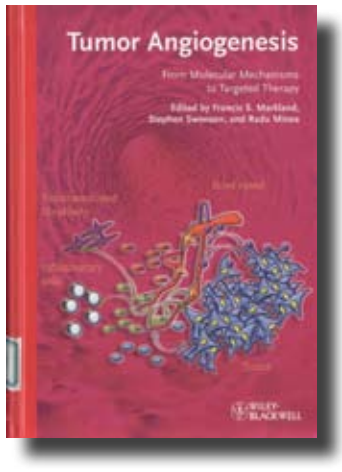
Many of us are familiar with the Maillard reaction. It gives cooked foods their colours and aromas, causes steaks to brown, and gives fish and chips their signature flavours. Unfortunately, it is also responsible for unwanted compounds such as acrylamide and ammonia. Many of its side-products are implicated in inflammation, diabetic nephrology and ageing. They are also robust markers for many diseases, such as Alzheimer's and atherosclerosis. While these features make the Maillard reaction important to study, its potential to generate complex side-products makes this difficult.

The Maillard Reaction: Recent Advances in Food and Biomedical Sciences is a wonderful resource for reviews on every aspect of the reaction. At the outset, it is deceptively simple: the exposed aldehyde group of the open-chain form of sugars reacts with the primary amine groups of amino acids. However, the Schiff base reaction product is unstable and quickly rearranges into a host of different chemicals, each with their own downstream reaction products. They can also form crosslinks with free and peptide-bound amines, yielding complex aggregates and polymers. The result, even for the relatively simple glucose, is a massive network of reaction pathways. While this has been known since the 1950s, the biological significance of the individual products is still being elucidated, compound by compound. A battery of biochemical techniques and technologies is required simply to isolate the chemicals.

One of the most valuable features of the book is the description of novel mass spectrometry and high performance liquid chromatography methods to analyse the reaction products. Efforts to chemically synthesise products are also described. In addition, clinically significant associations of the reaction products and their protein receptors are exhaustively detailed. The book even has tips on how to minimise acrylamide content when frying chips! Unfortunately, I felt that the organisation of the book could be improved. For example, it might be easier for a reader if papers were grouped into themes, such as isolation of reaction products or implications for diabetes. Nonetheless, for a motivated researcher, this book is a treasure trove.

Tumor Angiogenesis: From Molecular Mechanisms to Targeted Therapy

Edited by Francis S Markland, Stephen Swenson and Radu Minea
Wiley-Blackwell, 2010
(Reviewed by Jennifer de Beyer)



The discovery that tumours can attract endothelial cells to form their own blood vessel network, a process called angiogenesis, gave cancer treatment a new direction. When angiogenesis is inhibited, the nutrient supply to the tumour is cut off, leading to tumour shrinkage and failure. *Tumor Angiogenesis: From Molecular Mechanisms to Targeted Therapy* describes recent progress in understanding angiogenesis and its inhibition.

The text covers the mechanisms of angiogenesis, focusing on the signalling molecules used by both the body and the tumour to promote angiogenesis; the progress made in the development of anti-angiogenesis compounds; and the tumour imaging techniques used to study the effects of these compounds.

The book is more a collection of reviews than a coherent textbook. There is some overlap between the introductory sections of each chapter but most focus on primary research, highlighting the latest results. Every chapter includes an in-depth discussion of the clinical implications of the mechanisms discussed and areas for further study. Those who enjoy their physiology with lavish illustrations are likely to be disappointed as the graphics are both minimalist and infrequent, with the exception of the imaging chapters.

The text is ideally suited as an update on tumour angiogenesis research for cancer researchers of all biological backgrounds. However, the focus on primary research and level of detail would prove challenging for those looking for an introduction to the field. With the amount of space dedicated to clinical applications and discussions of the available drugs for targeting angiogenesis, it would also be useful for oncologists and other medical professionals. Unfortunately, it is likely to date quickly as a reference text due to the speed at which this field progresses.

Some common responses to the *OneOak* tree felling

- "How can cutting down a tree that is older than 100 years be 'sustainable'?"
- "You are destroying wildlife."
- "Why did you have to cut it down - was it diseased or dangerous?"

Wood culture

Modern society is becoming increasingly removed from the natural world and, although we still use many wood products, some people do not welcome tree felling or management activity in our woodlands. Yet timber is Britain's sixth largest import, with over one million tonnes of hardwoods imported every year. Producing more home-grown timber would be good for local economies, and have a positive effect on the health of our woodlands (1). Achieving this is difficult in the face of public antagonism towards woodland management. It may not be an exaggeration to say that Britain has lost its 'wood culture'. As the second least-wooded country in Europe (12% cover), Britain's forests are important for a wide variety of reasons, including the diversity of landscape, wildlife, ecosystem functions (e.g. flood control and local climate control), recreation, health, and of course timber and wood fuel.

Local schoolchildren

Oxfordshire-based tree and forestry charity, The Sylva Foundation (2), established the *OneOak* project in 2009 in an effort to convey the benefits of growing trees for timber. Sylva decided that telling the stories behind the life of a single oak tree would be a powerful way of communicating the often complex nature of sustainable forestry. A mature oak tree on the Blenheim Estate in Oxfordshire was selected for the project. Working with local schools, artists, wood users and scientists, various activities were initiated to try to promote forestry in a positive way through science, art, crafts and active education.

The *OneOak* tree was felled on a freezing day in January 2010, witnessed by 250 children and 150 guests. It has now become one of the most studied trees in Britain thanks to work by a dozen scientists exploring its size, volume, weight, carbon profile and age.

The *OneOak* tree at the Blenheim Estate.

THE LIFE STORY OF ONE OAK TREE

Dr Gabriel Hemery, Chief Executive of the Sylva Foundation, describes their work promoting sustainable forestry in the UK.

Science

Scientists from the UK government's Forest Research visited the tree before it was felled to take a number of measurements, including tree height (24 m), stem diameter (90 cm) and crown diameter (17 m). A camera with a hemispherical lens was used to capture the tree's canopy, which was analysed to estimate the size of the crown area and the leaf area per area of ground, which are key determinants of the tree's light interception and growth.

An unusual sight in a woodland, laser scanning was carried out prior to felling, using a Leica C10 Laser Scanner which was placed at five different sites around the tree. Laser reflection data from these different positions were merged to produce a detailed digital 3D virtual model of the tree, which is available on the *OneOak* website.

Immediately after felling, the tree was prepared for the massive effort of weighing and measuring all its above ground components. The main stem was cut into three sections and weighed using a weighbridge. The fresh (or green) weight of the crown was measured by weighing every branch, limb and twig using a spring balance. After oven-drying samples of different components, the total dry weight of the tree, including an estimate of the root weight, was calculated to be 9.92 tonnes.

involved in the project.

Leading dendrochronologist Dr Daniel Miles, from the Oxford Dendrochronology Laboratory, collected seven discs from the main tree stem and from one branch immediately after felling. The original estimate that the tree was about 160 years old, based on estate records, proved to be a considerable underestimate. The lowest disc, taken about 30 cm above ground level, suggested that the tree was 30 cm tall in 1790. Therefore the tree probably germinated in 1788, making it 222 years old when felled in 2010.

Wood

Thirty-five oak boards were cut from the three main sections of the *OneOak* tree by a local sawmill. These are currently air drying prior to use by dozens of Oxfordshire wood users who will make items during 2011 and 2012, ranging from fine furniture, a door, a boat, and a beam in an oak-framed building, to green working and crafts, and even firewood. Some of these products will be followed in detail to calculate their carbon footprints by Oxford-based specialists Best Foot Forward.

Transporting the *OneOak* timber.

Education

Five Oxfordshire primary schools have been involved in the *OneOak* project. In Autumn 2009, 250 children spent a day conducting scientific studies of the tree, art and maths activities, and bug hunts in the woodland around the tree. They returned to watch the tree felling in January 2010, and furniture design students from Oxford and Cherwell Valley College have been working closely with the children to design outdoor benches for their schools. This January, they returned to the woodland at Blenheim Estate to each plant a new oak, making a 'forest' of 250 seedlings.

Communications

The *OneOak* project has an active website (www.OneOak.info) where all the scientific data are available along with several films, stunning original art and more. Several exhibitions are planned for 2011 and 2012, including at the University of Oxford Botanic Garden from April - September 2011, and at the Museum of Natural History from October 2011 - January 2012.

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Translating Science

Lisanne Stock discusses the difficulties in conveying scientific research to the public.

After flipping through a Saturday morning tabloid, watching a TV science programme, or even reading science blogs, one often comes away with a feeling that the presentation of scientific research to the public can be significantly delayed or distorted. Many studies have been extremely under-publicised, in some cases contributing to preventable deaths. Perhaps particular subjects don't make the headlines because they are deemed less attractive or lucrative, despite their importance. Undeniably, scientific advances concerning breakthroughs in areas such as cancer treatment often grace the front pages. Yet, many scientific advances which could directly impact individuals' lives are not publicised for considerable amounts of time, if ever. In fact, preventing delays in the relay from research to public media can be lifesaving. One only has to look at the effect of the book *Baby and Child Care* by Dr Benjamin Spock (first published in 1946), thought to be responsible for thousands of cot deaths due to misguided advice on positioning babies on their fronts during sleep (1). This practice continued until 1991 despite the availability of evidence since the early 1970s that it was safer to place babies on their backs. For me the key question is why the public were not told about this sooner as it could potentially have saved 12 avoidable cot deaths a week for the better part of two decades?

Rather than working as separate entities, wary of one another, science and the media could profit from a closer relationship. Part of the reason it is so hard to achieve greater mutualism between science and the media is because science can seem inaccessible, a language in itself. The philosopher Ludwig Wittgenstein would agree that science is a 'language-game' (2). Science is intricate, with specific dialects and colloquialisms within subjects; a molecular physicist would not be expected to be completely *au fait* with the work of an immunologist. The skills needed to decipher the work of scientific specialities are part of a subject's beauty, but this requirement can pose a challenge when transferring scientific advances to a wider audience. Science journalists are employed as general factotums. They are usually expected to cover a wide range of subjects and it is not feasible to be a true expert in all of them. One week they may be writing an article on the effects of phone radiation, whilst the next they may be inquiring into the mating habits of antelopes (surprisingly for some, a truly intriguing subject), and this lack of specialisation may lead to miscommunication of crucial scientific information.

It is important that readers are aware of distorted statistics, tweaked titles and irrelevant information used to 'spice up' the content of an article. However, apart from a few eager and erudite philomaths ready with a copy of *Science* on a salubrious Saturday morning, many members of the public may have last contemplated scientific problems as schoolchildren preparing for their GCSEs. Thus, the public simply lack the specialised training and the 'language skills' needed to decipher complex scientific techniques, such as molecular cloning, unless explained to them from first principles. However, very many 'laypeople' are curious and eager to learn about science, which can provide a good starting point for the communication of important scientific advances to the general population.

Charities such as Sense About Science aim to equip people with information to evaluate scientific evidence, and help them to respond to areas of misconception such as the dangers of genetically modified crops and carcinogens. The charity also pioneers initiatives such as the Voice of Young Science Network and Science for Celebrities. In the latter project, the Sense About Science study cites the actress Juliette Stevenson who gave her views about immunising her daughter with the MMR vaccine to a Sunday newspaper, saying: "I was alarmed at the idea of three diseases being injected into her system in one go. I thought, bloody hell, that's an awful lot for this tiny thing" (3). Such comments by celebrities can hugely influence important decisions made by members of the public. Thus, not only must we be concerned with encouraging the positive representation of science within the media, but it also seems desirable that the media should be actively involved in exposing such claims made by influential people as false before they are splashed on the front

pages. There is the glaring example of the hugely controversial and misleading study by Dr Andrew Wakefield, which incorrectly suggested there may be a link between the MMR vaccine, and autism and bowel disease (4, 5). The resulting panic by some parents meant that large numbers of children did not receive the MMR vaccine, potentially allowing a resurgence of these deadly infectious diseases. Subsequently, Dr Wakefield became a pariah of the medical profession, showing that there can be consequences to manipulating the media.

The Science and Media Centre acts as a press office for the main newspapers and works to "promote the voices, stories and views of the scientific community to the national news media when science is in the headlines" (6). They provide a forum where journalists can ask about specific scientific issues in an attempt to equip them and via them, the public, with tools for understanding and independently evaluating scientific evidence. Progress is being made to correctly present science to the public, with programmes such as the BBC's *Health Check* becoming a staple TV viewing for many members of the public. The website EurekAlert! is also a great source for getting to grips with breaking scientific news and is constantly updated with press releases and articles concerning advances at the forefront of science (7). Additionally, amongst the media there are several pioneering figures, such as journalists Simon Singh and Ben Goldacre, who through their many books and columns are helping to bridge the gap between scientists and the public.

Undoubtedly, the relationship between science, the media, and the public is complicated. Science seems to have acquired a certain patina for the general population. However, successful communication of scientific data is beneficial to everyone, and needs to be improved.

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5'WITH... Professor Jordan Raff

Interviewed by Nicola Platt

Jordan Raff was welcomed to the Dunn School of Pathology as Milstein Professor of Molecular Cancer Biology in August 2009, having moved his group from the Gurdon Institute in Cambridge. His lab focuses on the role of centrioles and centrosomes at the molecular level, using* Drosophila melanogaster *as a model.

When did you first decide you wanted to be a scientist?
My dad was a well-known scientist so I could always see it was a rewarding and worthwhile career; however, I never planned to become one. I mistakenly thought I was very creative and tried to get into advertising. I worked in advertising for one day and hated it, so applied for a PhD position instead. It wasn't straightforward though; I applied for more than eight PhDs before I was accepted.

If you were not a scientist you would be...
A professional footballer...although I realise my chances of achieving this are getting low!

If you are not in the lab you are...
Looking after the kids, cooking, cleaning, chauffeuring them around...but I wouldn't change it for anything. It's better than being in the lab!

What has been your worst disaster in the lab?
One weekend I was alone in the lab, using a machine that makes oligos (back when each lab made their own). The gas cylinder supplying the machine ran out and I did not know how to change it. Whilst attempting to do so, the gasket blew. The cylinder was shaking violently and making such a noise that people came running from floors around. I was lucky it was chained in place or it could have been incredibly dangerous.

What has been the most important moment of your career so far and have you any particularly memorable findings?
My most memorable moment was during an experiment investigating *Drosophila* embryonic cell division. I remember looking down the microscope watching the embryo in real-time. I had blocked nuclear division, yet centrosomal division continued, showing that this alone was sufficient to drive cell division and the production of pole cells. I remember being amazed at this discovery and realising that, at that moment, I was the only person in the world who knew what centrosomes could do. It was at this moment I decided on the future of my work - studying centrosomes.

What is your favourite conference location?
San Francisco. I worked there as a postdoc for five years and it is an incredible city. You must visit it if you ever get the chance.

What is the best advice you have ever received?
I was once told to worry only about the things you can change. Worrying about anything else is a waste of time and energy. Suppose a competitor's paper is accepted for publication in *Nature* when you feel it is flawed. There is no benefit in fretting or agonising over it. You cannot change it, so it is far better not to dwell on it.

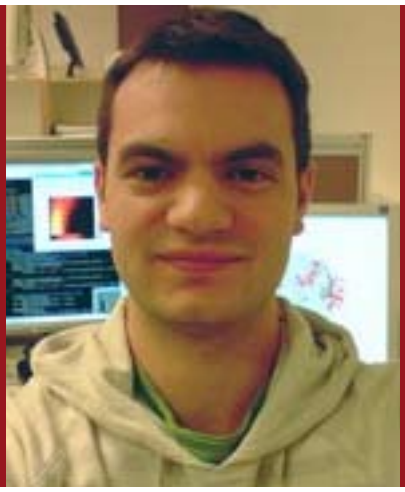
If you were starting your career again are there things you would do differently?
No. My career certainly hasn't been perfect but I would not change anything. I'd rather have my life than a different one.

Do you have a favourite classical experiment?
In physics, when light is passed simultaneously through small slits, it forms diffraction patterns, suggesting that light behaves as a wave. However, the same diffraction patterns are seen even if the light is passed through the slits a single photon at a time, such that there is no way they can interact with one another. I think this is so cool, I just cannot get my head around how light can function as a particle and yet form patterns such as these, behaving as a wave.

In your opinion what makes a good scientist?
You have got to be optimistic in everything except in interpreting your own results. You must be a 'glass half-full' person or I think you would quickly become demoralised. However, when it comes to your own results you need to resist the temptation to read more into them than is there. You need to be sceptical and the toughest critic of your own work.

How do you imagine biological research will change over the next 20 years?
I think the biggest change is that nearly everyone will have their genome sequenced, probably within the next 5-10 years. Mining this information will be incredibly effective in ways we cannot yet predict. However, I think this is really frightening because, as a society, we have not thought about the consequences of mass sequencing thoroughly and, given how quickly technology is advancing, we are unlikely to do so before this becomes a reality. I also worry this will change the way in which we do biological science, from curiosity-driven experiments to simply processing large volumes of data and information.

SNAPSHOT Research Image Competition



We are very pleased to announce that this issue's winner of the *Snapshot* scientific image competition is Daniel Parton, a final year DPhil student in Professor Mark Sansom's group in the Department of Biochemistry.

This image was created from recent simulations of the influenza virus envelope, which aim to elucidate the viral assembly mechanism focusing on the lateral organisation of the viral membrane.

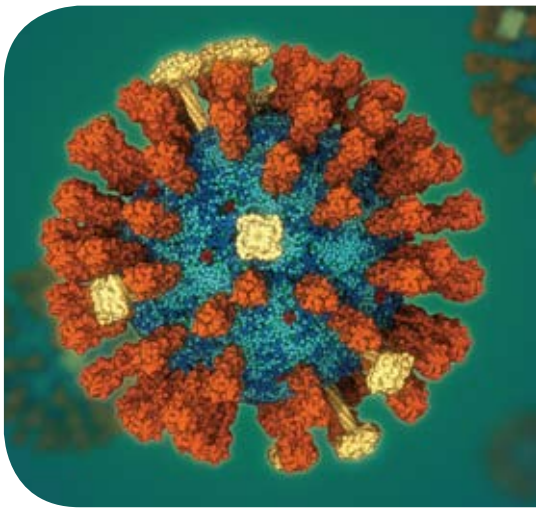
In recognition of his contribution, he will receive a £50 book voucher, kindly provided by our sponsor Oxford University Press.

We hope he will enjoy his reading!

The influenza viral envelope comprises a lipid membrane with three types of embedded proteins: haemagglutinin (HA) in orange, neuraminidase (NA) in white and the M2 ion channel in red. The function of HA is to target and bind the virus to the host cell membrane, with the aid of the M2 channel, which helps to release the viral RNA into the cytoplasm, while NA facilitates the release of nascent virions.

This model represents the membrane lipid composition with a ternary mixture: saturated phospholipid (di-16:0-PC) in light blue, unsaturated phospholipid (di-linoleoyl phosphatidylcholine; di-18:2-PC) in dark blue and cholesterol in green. The model is constructed with realistic dimensions and protein stoichiometries.

The influenza viral envelope is an extremely large system to attempt to simulate, so Daniel uses a coarse-grained model, in which each particle corresponds to approximately four heavy (non-hydrogen) atoms. However, the solvated system still comprises five million particles (equivalent to ca. 60 million atoms), meaning that supercomputers in France and the UK have been vital for conducting the simulations. The images were then imported into the Visual Molecular Dynamics programme, which allows molecules to be represented in a number of different ways, as well as state-of-the-art rendering techniques such as ambient occlusion.

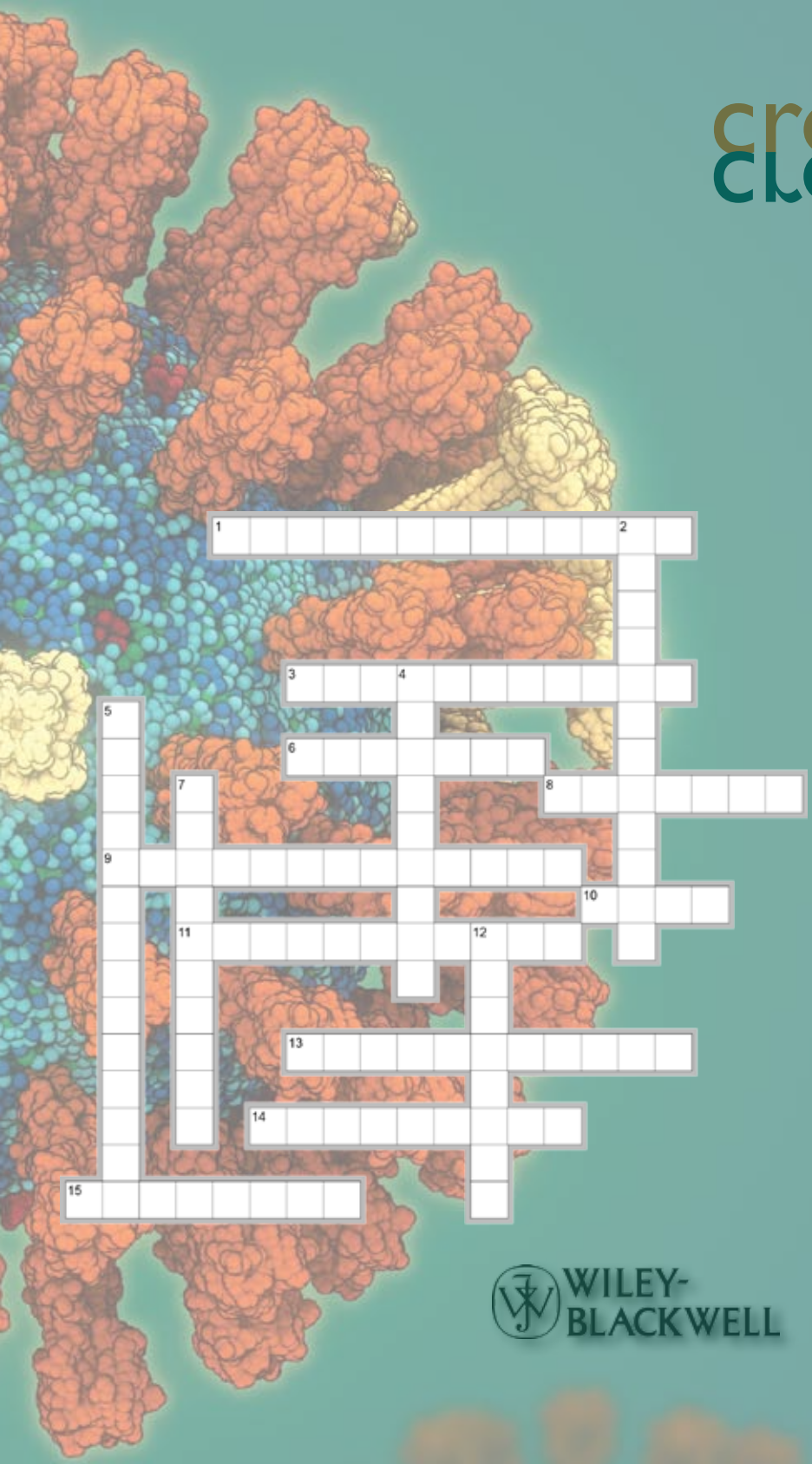


These simulations hope to provide an insight into the structure of the viral envelope and the mechanism of its assembly. Prior to the formation of a new virion, the viral components are thought to assemble at the host cell plasma membrane as 'membrane rafts'. These rafts are small, ordered domains enriched in sphingolipids, cholesterol and certain proteins. However, these rafts have not yet been observed directly in cell membranes, and studies using model membranes have not been able to show how the influenza proteins are targeted to ordered membrane domains. Accurate simulations of the viral envelope, such as Daniel's, can therefore overcome some of the difficulties associated with these models. Early results indicate that the high concentration of proteins in the viral envelope induces phase separation of the lipid membrane into ordered and disordered domains, suggesting how the proteins might self-assemble into rafts.

Therapies for influenza may be developed based on the understanding of this mechanism, such as strategies targeting the viral assembly process. It may also have implications for processes such as signal transduction and protein trafficking of other membrane proteins.

Snapshot Michaelmas 2011: how to enter...

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 in Phenotype Michaelmas 2011. To enter, send pictures 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 25 July 2011.



crossword

Test your knowledge of the immune system with this term's *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 2 September 2011 will be entered into the prize draw.

The winner will receive their choice of two Wiley-Blackwell textbooks reviewed in this issue.

Congratulations to Martin Krehenbrink from the Department of Biochemistry who won the Hilary '11 crossword competition.

Across:

1. The treatment of diseases by actively modulating the immune response (13).
3. The administration of antigenic material to stimulate immunity to a disease (11).
6. The French scientist who was the first to artificially attenuate a microorganism for use in a vaccine (7).
8. The generic name for a molecule that contains an epitope recognised by the immune system (7).
9. A type of cytotoxic lymphocytes that were discovered through their ability to lyse cancer cells without having been sensitised to them (7, 6).
10. Acronym for the collection of diseases that occur due to infection by a virus that attacks the immune system itself (4).
11. A group of glycoproteins named after their ability to disrupt viral replication within host cells (11).
13. Granulocytes named after their lack of strongly basic or acidic granules, resulting in their poor staining by heamatoxylin and eosin (11).
14. Granulocytes that contain heparin and histamine, and have cell surface receptors for IgE (9).
15. Glycoproteins composed of various numbers of heavy and light chains (8).

Down:

2. The process by which cells engulf microorganisms and dead cells (12).
4. Secreted proteins that act as the 'signalling molecules' of the immune system (9).
5. Synonym for 15 across (14).
7. Generic name for diseases that occur when the host's immune system attacks the host's own tissues (10).
12. Molecules that coat microorganisms and enhance their recognition by immune cells (8).

WILEY-BLACKWELL

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