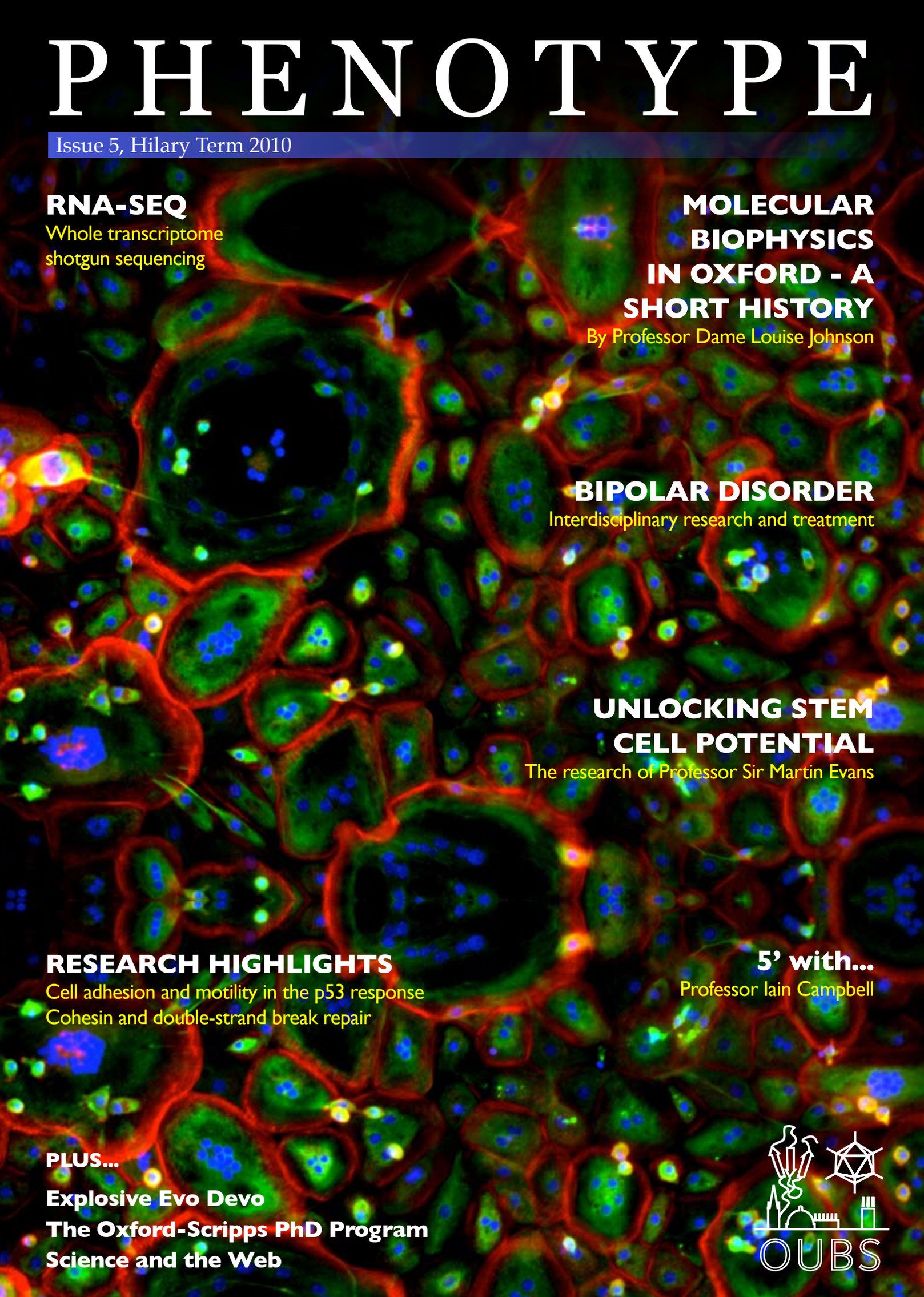
PHENOTYPE

Issue 5, Hilary Term 2010



RNA-SEQ
Whole transcriptome shotgun sequencing

MOLECULAR BIOPHYSICS IN OXFORD - A SHORT HISTORY
By Professor Dame Louise Johnson

BIPOLAR DISORDER
Interdisciplinary research and treatment

UNLOCKING STEM CELL POTENTIAL
The research of Professor Sir Martin Evans

RESEARCH HIGHLIGHTS
Cell adhesion and motility in the p53 response
Cohesin and double-strand break repair

5' with...
Professor Iain Campbell

PLUS...

Explosive Evo Devo
The Oxford-Scripps PhD Program
Science and the Web

OUBS

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OUBS

Editorial

Welcome to the fifth issue of *Phenotype*. The magazine has undergone a transformation since the Michaelmas '09 edition. *Phenotype* is now a university-wide publication devoted to biological sciences and biochemistry.

In the next few months Oxford University Biochemical Society is privileged to host talks by three Nobel Laureates. The first is Professor Sir Martin Evans from Cardiff University, one of the pioneers of mouse genetic modification. In our *Featured Seminar* article, Daniel Grimes discusses Evans' work.

Our *Features* articles explore some cutting edge research topics. Penny Sarchet tells us about her research into the genetic basis of pod shatter and seed dispersal in *Cardamine hirsuta*. Anna Boleininger reviews RNA sequencing, a technology that could revolutionise transcriptome analysis, a major challenge in understanding how gene sequences relate to observed phenotypes. Finally, James Halstead investigates what biochemistry has to offer the study and treatment of bipolar disorder.

Oxford has a strong track record in structural biology. Professor Dame Louise Johnson gives us a fascinating insight into the development of molecular biophysics at the university. This issue's *5' with...* features Professor Iain Campbell, who helped to establish NMR in the Biochemistry Department in the 1970s and now works on the structure and dynamics of integrin adhesion complexes.

If you'd like to write an article for the Trinity 2010 issue of *Phenotype* please get in touch. You can write about your own research, an area that interests you, or review a book or exhibition. New ideas are always welcome!

Finally, I would like to thank Professor Edith Sim and the Medical Sciences Division Skills Training Fund for their support. They have made it possible for us to print a large number of copies of this issue.

David Yadin
Editor

Did you know that you can view the latest issue of *Phenotype* online?

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Contents

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The deadline for article submissions is Friday 12 March 2010.
We accept articles on any aspect of biological sciences research, books or science education.
Articles can be either 600 or 1200 words.
If interested, please get in touch (oubs@bioch.ox.ac.uk).

Work for *Phenotype*?

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

OUBS Seminars

Hilary 2010

Friday 15 January
Dr David Keays
Institute of Molecular Pathology, Vienna
"The molecular basis of magnetoreception"

Monday 18 January
Prof. René Medema
University Medical Center Utrecht, Netherlands
"Recovery form a DNA damage-induced arrest"

Monday 25 January
Dr Rik Korswagen
Hubrecht Institute, Utrecht, Netherlands
"Mechanism of Wnt secretion"

Monday 1 February
Prof. Julian Blow
Wellcome Trust Centre for Gene Regulation and Expression, Dundee
"How S phase is organised to ensure complete genome duplication, and why cancer cells might get it wrong"

Monday 8 February
Prof. Martin Warren
School of Biosciences, University of Kent
Title to be confirmed

Monday 15 February
Dr Geneviève Almouzni
Institut Curie-Recherche, Paris, France
Title to be confirmed

Monday 22 February
Dr Fiona Watt
Cancer Research UK Cambridge Research Institute
Title to be confirmed

Monday 1 March
Dr Magdalena Zernicka-Goetz
The Gurdon Institute, University of Cambridge
Title to be confirmed

Wednesday 3 March
Prof. Sir Martin Evans FRS DSc
Winner of The Nobel Prize in Medicine 2007, Cardiff School of Biosciences, Cardiff
Title to be confirmed
Special Nobel Laureate Lecture, more details to follow soon.
A joint event between the Oxford University Biochemical Society and the Oxford University Scientific Society.

Monday 8 March
Dr Marc Bühler
Friedrich Miescher Institute for Biomedical Research, Basel
Title to be confirmed
Sponsored by the RNA Society
http://rnasociety.org/

Wednesday 17 March
Prof. Angelika Amon
Massachusetts Institute of Technology, Cambridge, USA
Title to be confirmed

Everyone is welcome at the 15th OUBS Annual Careers Day

A day of short, informal talks

Date: Tuesday 9 February 2010
Time and Venue: 12-5pm, Med. Sci. Teaching Centre Lecture Theatre
Food and drink wil be available, including lunch.

We aim to provide information about some of the varied careers available to science graduates.
Careers represented in this year's event will include: academic research, science communication, science journalism, teaching, graduate-entry medicine, patent law, consulting, finance and pharmaceuticals.
For further information please visit our website:
http://www4.bioch.ox.ac.uk/oubs/careersday.php

UNLOCKING STEM CELL POTENTIAL

On 3 March 2010, Professor Sir Martin Evans from Cardiff University will speak in Oxford as part of the 'OUBS Nobel Laureate Lecture Series'. Daniel Grimes reviews Evans' seminal work.

Today, genetically modified mice are used in basic research, as models of human disease and for drug testing and discovery. Large international projects are underway to knock-out every protein-encoding gene in the mouse genome, and thousands of laboratories across the globe use gene targeting technologies to create designer mice harbouring specific genetic alterations. Similar technologies are now being pioneered on human cells, with boundless implications for the treatment of previously incurable diseases.

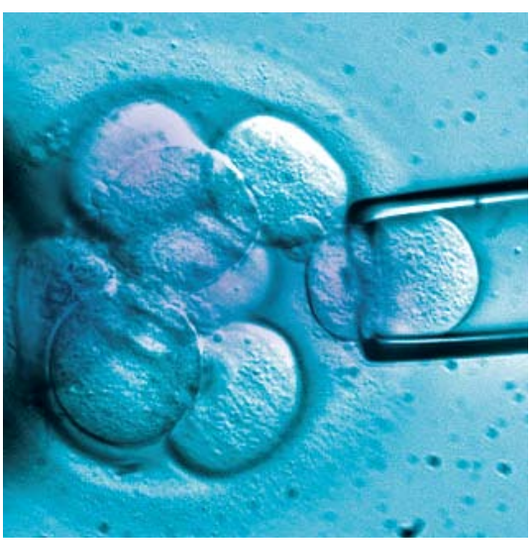
The technology used to genetically modify mice makes use of the properties of a very special breed of cells – embryonic stem (ES) cells. ES cells, found in early embryos, are special because of their unique ability to differentiate into all other cell types of the adult body. This means that ES cells can be used to make an entire organism, such as a mouse, where every cell is derived from ES cells cultured in the laboratory. By altering the genome of ES cells at the culture stage, these cells can then be transferred to a host embryo and thereby used to make a mutant mouse containing the desired genetic change.

Used routinely today, the development of the technology to create genetically modified mice required a number of scientific advances, including the seminal discoveries of Martin Evans. Evans' breakthrough was in figuring out how to derive ES cells from normal embryos and culture them *in vitro* in such a way that they maintain their potential to differentiate into all other cell types. Importantly, Evans realised that ES cells require growth on a 'feeder layer' to survive indefinitely in culture.

Evans' team went on to streamline methods for injecting ES cells into embryos and thereby created the first cultured ES-cell derived mice. Crucially, they were able to show that mutations introduced into ES cells during the culture phase could be carried through the germline of the manufactured mice. In this way, using retroviral-mediated mutagenesis, Evans and colleagues generated lines of mutant mice from ES cells. They also isolated ES cells containing a retroviral insertion in the *Hprt* gene, which encodes the hypoxanthine-guanine phosphoribosyltransferase enzyme essential for purine synthesis. Moreover, the team went on to make the first ES-cell derived knock-out mouse in which Hprt was completely inactive. These seminal breakthroughs revealed how to make mice using cultured ES cells, and provided a proof-of-principle that genetic mutations introduced into ES cells could be transmitted to the resulting mice and importantly, their offspring.

Whilst retroviral-mediated mutagenesis had been a powerful tool for disrupting genes, these modifications were random and dependent upon where the viral sequence integrated into the genome. During the 1980s, when Evans was revolutionising stem cell technology in Cambridge, two Americans, Mario Capecchi and Oliver Smithies, were beginning to understand that genomes could be mutated in a much more reliable and specific manner using homologous recombination – switching wild-type sequence for mutated sequence. Fusing the work of Evans, Capecchi, and Smithies gave us a method for specifically mutating genes in cultured ES cells, then building mice using these cells. The technique, now called 'gene targeting in embryonic stem cells' opened the floodgates to genetic manipulation of mice.

We now have experimental tools for creating a plethora of designer mice – gene knock-outs, conditional mutants, gene reporter alleles and many more. Rather than relying on spontaneous mutations to work out gene function, we have the ability to systematically target genes and assess their roles. The 2007 Nobel Prize in Physiology recognised the breakthroughs of Evans, Capecchi, and Smithies who combined molecular biology, genetics, and sophisticated embryology and unlocked the potential of ES cells to study, in exceptional detail, the function of any gene in a living animal.



Embryonic stem cells: a valuable tool for genetic research.

A transcription co-factor integrates cell adhesion and motility with the p53 response

Amanda S. Coutts, Louise Weston, and Nicholas B. La Thangue. *Proc Natl Acad Sci USA* 106, 19872-7 (2009)

Cell motility plays a key role in allowing tumour cells to invade and colonise healthy tissue. JMY (Junction-mediating and regulatory protein) was previously identified as a transcription co-factor that modulates p53 activity during the DNA damage response. This study investigated how JMY influences cell motility.

Cadherins are responsible for cell-cell adhesion, which is closely linked to cell migration and invasion. In this study, JMY siRNA-treated MCF-7 cells showed reduced motility and increased E-cadherin expression. The motility effect was rescued by simultaneous depletion of E-cadherin, indicating that JMY regulates cell motility via cadherin.

JMY depleted-MCF-7 cells displayed reduced migration into wound site. Conversely, wound healing was enhanced following induction of ectopic JMY. Healing rates were dependent on the actin-binding WH2 (Wiskott Aldrich Syndrome protein-homology) domains, located in the C-terminal region of JMY. G-actin incorporation assays showed that JMY can direct actin incorporation at its intracellular locations, mediated by the WH2 domains. This indicated that JMY influences cell motility through effects on the actin cytoskeleton.

The activity of p53 in U2OS cells was reduced following JMY depletion, and enhanced following induction of ectopic JMY. It was demonstrated that JMY undergoes nuclear accumulation in response to DNA damage, leading to the activation of p53. When actin polymerization was blocked, however, JMY could not activate p53.

Coutts *et al.* have therefore identified a pathway that links the cytoskeleton with the p53 response. This suggests that JMY-mediated control of cadherin and actin is pivotal in coordinating cell motility with p53 activity.

Cohesin promotes the repair of ionizing radiation-induced DNA double-strand breaks in replicated chromatin

Christina Bauerschmidt, Cecilia Arrichiello, Susanne Burdak-Rothkamm, Michael Woodcock, Mark A. Hill, David L. Stevens and Kai Rothkamm. *Nucleic Acids Res* (2009) Nov 11 (Epub ahead of print).

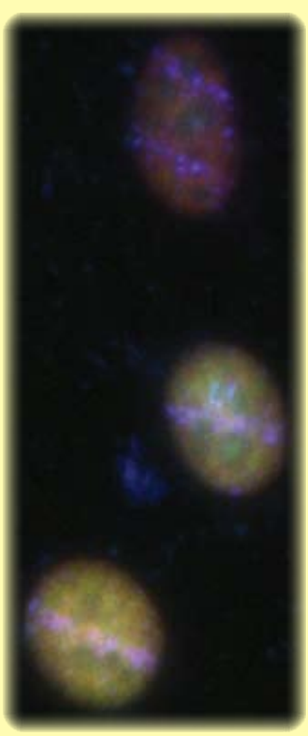
Following DNA replication, the cohesin protein complex holds sister chromatids together until mitosis and plays an important role in chromosome segregation. It is also believed to be involved in post-replicative DNA repair in yeast and higher eukaryotes.

Bauerschmidt *et al.* investigated the role of the cohesin subunits SMC1 and Rad21 in DNA double-strand break (DSB) repair in human cells. HeLa cells, depleted of SMC1 using siRNA, showed increased sensitivity to X-rays, indicating a role for SMC1 in survival of cells exposed to X-irradiation. Following X-irradiation, SMC1- and Rad21- depleted HeLa cells showed increased levels of DSBs, indicated by immunostaining for the DSB marker γH2AX. However, this effect was only observed in late S/G2-phase cells, not G1-phase, indicating that cohesin is required for DSB repair in replicated chromatin.

The DNA damage kinase ATM, but not DNA-PK, phosphorylates SMC1 following irradiation. Bauerschmidt *et al.* showed that inhibition of ATM or DNA-PK resulted in increased levels of DSBs. However, inhibition of ATM in SMC1-depleted cells, in G2-phase, did not result in a further increase in radiation-induced DSBs, indicating that cohesin and ATM may function in the same pathway. Conversely, the frequency of radiation-induced DSBs increased further following inhibition of DNA-PK in an SMC1-depleted background.

Using partially shielded soft X-rays, 1 μm wide 'stripes' of DNA damage were induced in HeLa cells. Immunofluorescence microscopy showed that Rad21 and SMC1 were recruited to the sites of DNA damage in G2-phase cells, but not G1-phase cells. However, the authors were not able to detect recruitment of other cohesin subunits to the DNA damage sites using the same method.

This study demonstrates that cohesin promotes the repair of DSBs induced by non-lethal radiation doses in human G2-phase cells, in an ATM-dependent pathway, but not in G1-phase cells.



The cohesin subunit Rad21 (Red) colocalises with the DNA damage marker 53BP1 (Blue) only in CENP-F-expressing (Green) S/G2 phase cells following irradiation with partially shielded ultrasoft X-rays.

Explosive Evo Devo:
Pod-shatter in *C. hirsuta*

Penny Sarchet

A rebounding "Thwack-ping!" is the sound of a greenhouse of a hundred and fifty mature *Cardamine hirsuta* plants expelling their seeds at over ten metres per second. This is explosive dehiscence – the active propulsion of a plant's offspring – and as a developmental biologist, I am seeking to uncover the genetic networks that bring about this process.

How do divergent morphologies evolve? This is a key question faced by evolutionary developmental biologists. The wide variety in form that we observe in nature - wing patterns, tail lengths, beak shape, body colour – all arise from a genetic basis. Aesthetics and art have long turned to plants for their wide variety of forms, from daisies to roses, and the extreme range of morphologies that a single homologous feature like a leaf or flower can exhibit renders plants a key resource for developmental biology too.

Divergent Morphologies *Arabadopsis thaliana* (left) and *Cardamine hirsuta* (right).

If we want to study genetics, we need a model, and for this we have every plant biologist's favourite weed, *Arabidopsis thaliana*. However, if we want to study genetic changes, we need something to compare our model to. In the laboratories of Miltos Tsiantis and Angela Hay we use *Arabidopsis* and its close relative *C. hirsuta* in parallel to investigate the genetic changes responsible for the differences in morphology between the two species. Together, *Arabidopsis* and *C. hirsuta* comprise a powerful comparative model, and have provided insights into the genetic basis of differences in leaf shape and floral form.

In Angela Hay's laboratory, we are now extending the use of this comparative model to fruit development, specifically seed dispersal. Whilst *Arabidopsis* disperses its seeds through a passive mechanism, whereby its seed pods ('siliques') split open when mature, exposing the seeds to wind, animals and gravity, *C. hirsuta* actively flings its seeds metres away from the parent. The evolution of this trait is extremely interesting – successful positioning of the next generation is of crucial importance to securing the continuation of a plant's genetic legacy, so must be under powerful selection forces.

The *Arabidopsis* and *C. hirsuta* siliques are very similar in overall morphology, but we have found that they differ markedly in a few ways. The replum, which forms the backbone of the silique, is much broader in *C. hirsuta*. This could be crucial for withstanding the greater pressures that must build in the explosive silique of *C. hirsuta*, and for influencing the behaviour of the other key silique tissue, the valve. In *Arabidopsis*, the valves span the majority of the silique, and seed dispersal occurs through the valves pulling away from the replum to create an opening. In *C. hirsuta*, however, the valves are flat and instead roll suddenly upwards, flinging the seeds lying beneath them out of the silique as they do so.

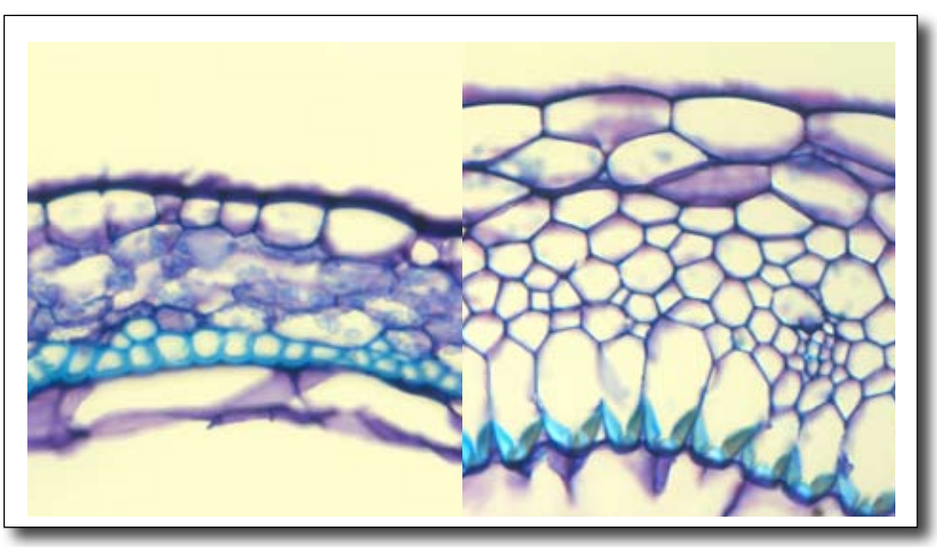
Lignification also differs between the two species' siliques. In *Arabidopsis*, the deposition of the woody polymer lignin in the silique has been well studied and is understood to play a key role in creating the tension required to pull the valve away from the replum. We have found that in *C. hirsuta*, there is not only a much greater quantity of lignin deposited, as one might expect in a more explosive process, but also that the pattern of lignification is different. Whilst the

Seed Dispersal *Arabadopsis thaliana* (left) and *Cardamine hirsuta* (right).

lignified cells in *Arabidopsis* possess a thin layer of lignin in every cell wall, *C. hirsuta* cells thickly lignify a single cell wall. Examples of asymmetry in animal development have been well studied and are known to be of crucial importance, but remain less understood in plants, so the polarised deposition of lignin that we observe is intriguing.

To test the role of the differences in replum morphology and lignification pattern in explosive pod shatter in *C. hirsuta*, we are using three approaches: forward genetics, reverse genetics, and biomechanical modelling. The forward genetics approach has centred on a mutant screen in *C. hirsuta* and has uncovered a range of mutants exhibiting reduced or expanded replum size and altered lignin deposition. Characterisation, mapping and cloning of these mutants should elucidate the role of these characters in explosive dispersal and reveal the genetic differences between *Arabidopsis* and *C. hirsuta*. Reverse genetics will be used to alter the function in *C. hirsuta* of genes known to regulate silique opening and seed dispersal in *Arabidopsis*. Our biomechanical modelling approach is proceeding through collaborations with Adrian Thomas's flight research group in the Department of Zoology and Yiannis Ventikos from the Department of Engineering Science. Using high-tech and innovative filming methods and mechanical modelling, we are working to quantify and test the physical parameters of explosive seed dispersal. Used together, these three approaches should help us uncover the genetic changes in *C. hirsuta* that have enabled it to acquire its explosivity.

Penny Sarchet is a second year D.Phil student in Dr Angela Hay's laboratory in the Department of Plant Sciences.



Polarised lignin deposition Toluidine-O staining of lignin (blue) and cytoplasm (purple). *Arabadopsis thaliana* (left) and *Cardamine hirsuta* (right).

Further Reading:

Canales, C, Barkoulas, M, Galinha, C, Tsiantis, M. (2009) Weeds of change: Cardamine hirsuta as a new model system for studying dissected leaf development *Journal of Plant Research*. pp 1-9.

Barkoulas, M, Hay, A, Kougioumoutzi, E, Tsiantis, M. (2008) A developmental framework for dissected leaf formation in the Arabidopsis relative Cardamine hirsuta *Nature Genetics*.

Hay, A, Tsiantis, M. (2006) The genetic basis for differences in leaf form between Arabidopsis thaliana and its wild relative Cardamine hirsuta *Nature Genetics*. 38 (8): pp 942-947.

RNA-Seq:

Whole transcriptome shotgun sequencing has the potential to revolutionise transcriptome analysis.

Anna Boleininger

Six years after the first complete draft of the human genome was released, the processes underlying the conversion of genetically encoded information into an observed phenotype are still poorly understood. Consequently, widespread use of gene modulation for human therapies such as cancer treatment[1,2] still requires major advances in genomics and transcriptomics.

A limiting factor is the availability of high-throughput cost-efficient technologies for DNA and RNA analysis. DNA microarrays are the standard technique for transcriptome study analysis. They are high-throughput and relatively inexpensive, but suffer two major difficulties associated with DNA hybridisation.

Firstly, cross-hybridisation leads to high background noise levels, rendering maximal resolution to only several base pairs. This makes the determination of exact 5' and 3' boundaries and splice sites of genes difficult.

Secondly, the dynamic range of two orders of magnitude in DNA microarrays limits the monitoring of gene expression levels[3]. While very rare transcripts remain undetected, highly abundant transcripts saturate the signal or the binding sites and may not be quantified accurately.

RNA-Seq combines second-generation high-throughput DNA sequencing techniques with whole shotgun transcriptome sequencing.

Second-generation techniques are much more cost efficient that traditional Sanger methods, and are based on sequencing-by-synthesis in a parallel format. While the throughput is 0.08 million base pairs per run for the Sanger-based ABI3730 XL (Applied Biosystems), it is around 1000 million for new generation instruments like the Genome Analyzer by Illumina[4].

The reason for such a drastic difference in throughput lies in the sequencing approach: using reversible chain terminators in sequencing-by-synthesis, the data collection and the complementary strand synthesis take place simultaneously and tens of thousands of different DNA fragments can be sequenced at the same time. The Sanger chain termination method, in contrast, is more time consuming because complementary strand synthesis, fragment separation and data analysis happen in a stepwise fashion.

RNA-Seq also has a much larger dynamic range than DNA microarrays. A recent study suggested a range of five orders of magnitude for mouse sequence reads[5].

In addition, second-generation sequencing techniques have very low levels of background, allowing for single-base pair resolution of transcript boundaries and the detection of rare or novel transcripts.

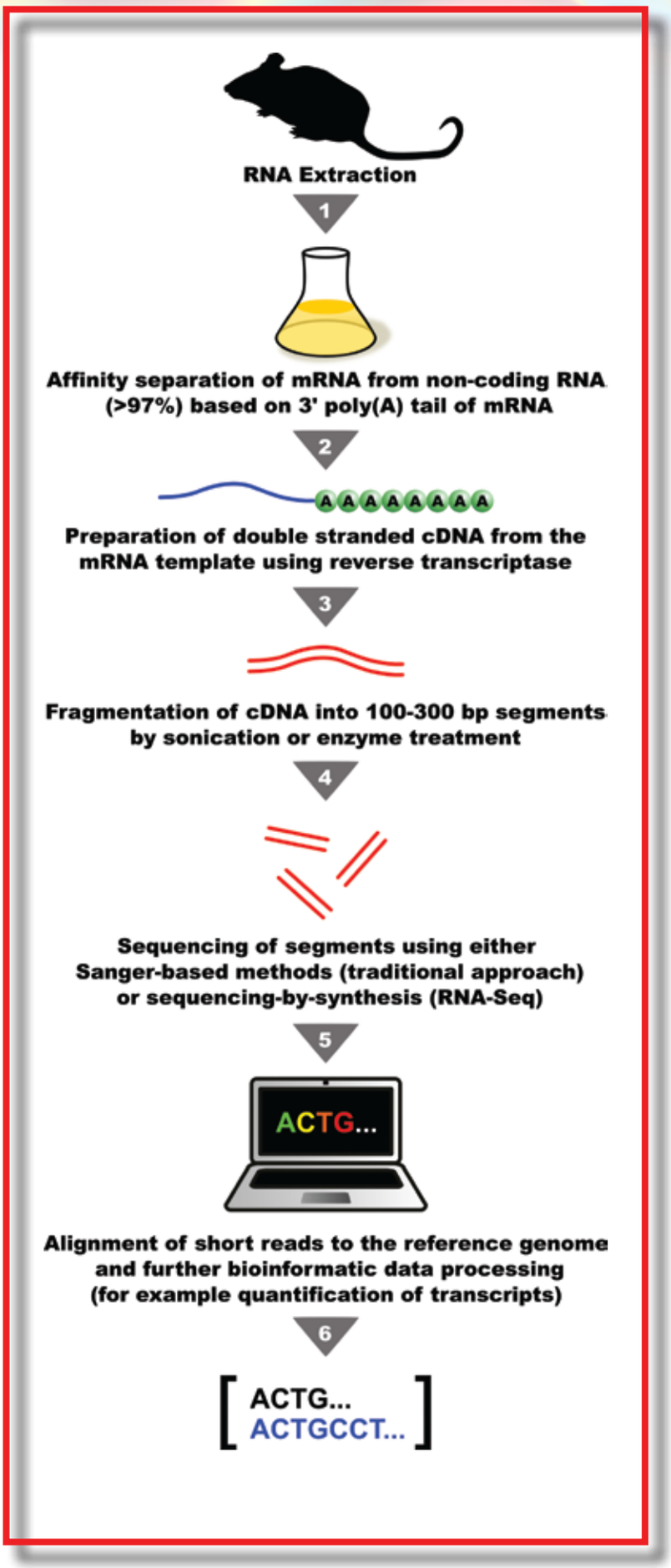
Nagalakshmi *et al.*[6] used RNA-Seq to obtain a high-resolution transcriptome map of *Saccharomyces cerevisiae*. Among many of the interesting findings of this work was that *S. cerevisiae* has far more original reading frames (ORFs) within 5' untranslated regions than previously thought. Many of these upstream ORFs precede genes that encode DNA binding proteins, suggesting that these sequences might be involved in regulating transcription factor expression.

While the presented research yielded very high quality data, RNA-Seq still faces some difficulties that must be resolved before becoming a standard technique.

Currently, the data analysis is far from trivial – the shotgun approach yields high numbers of short read lengths, associated with large amounts of data. The raw image files from one mammalian transcriptome run require terabytes of storage and processing presents a bioinformatic challenge[7].

Another important consideration is coverage versus cost. High coverage requires more sequencing depth (more base pair reads) and is needed for the detection of rare transcripts. Conversely, an increase in sequencing depth gives a larger amount of data to be analysed, invariably increasing the cost per run.

The large size of the human genome will lead to a very complicated transcriptome and require great sequencing depth in order to yield solid conclusions.



Despite these problems, RNA-Seq is expected to replace microarrays as a standard approach to transcriptome analysis. The difficulties relating to data handling and processing are expected to be overcome within a few years as information technology is developing very rapidly. The key task for the near future is to connect experts from the fields of molecular biology and biochemistry, genetics, statistics and computer science in order to create an optimised and uniform approach to experiments and data analysis.

Anna Boleininger is a second year D.Phil student in the Department of Chemistry.

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2. Immune modulation and graft protection by gene therapy in kidney transplantation, M Sandovici, LE Deelman *et al.*, *European Journal of Pharmacology* 2008, 585.

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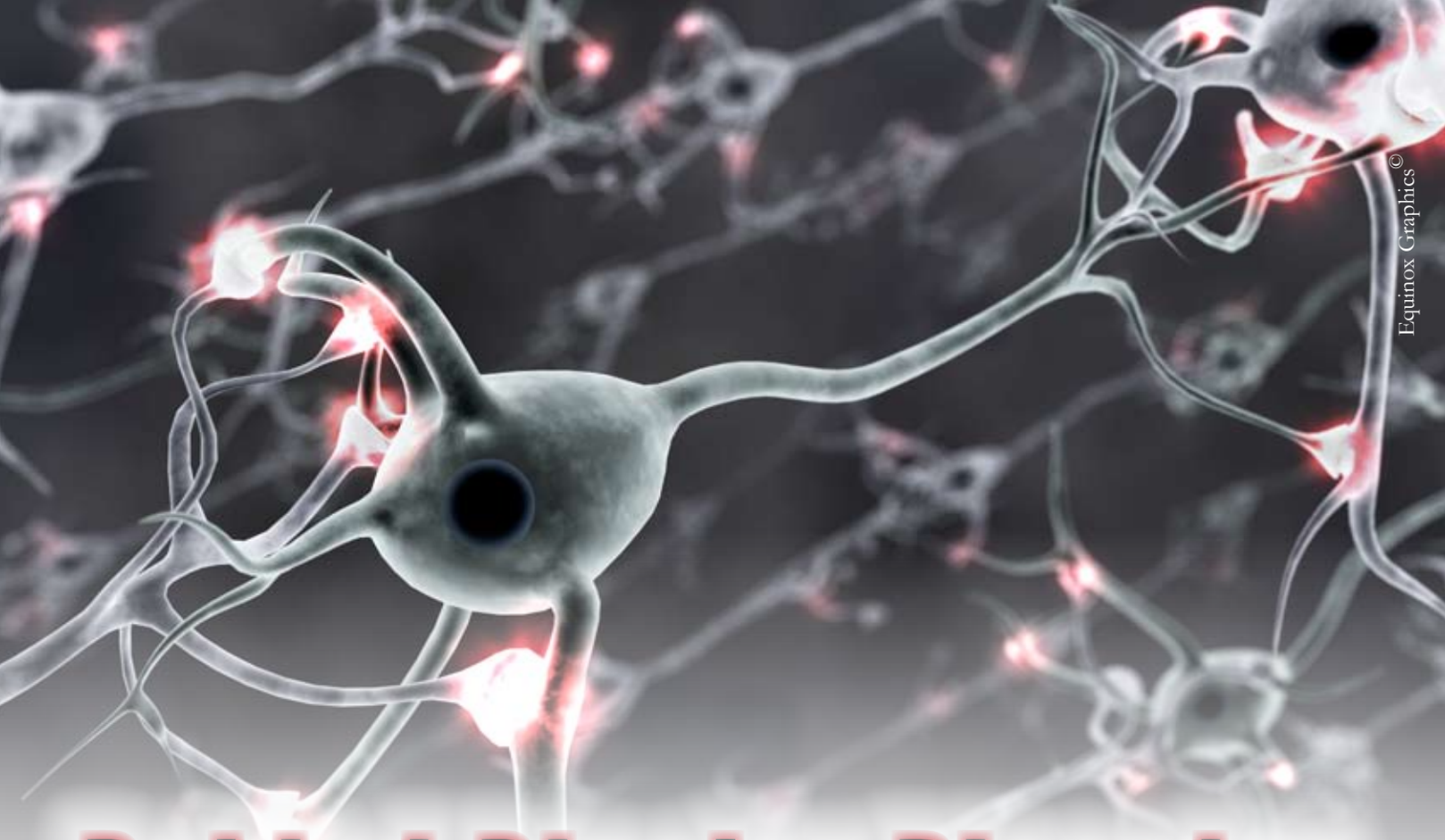


Behind Bipolar Disorder

James Halstead takes a look at how molecular biochemistry, statistical genomics and neurobiology may provide new therapies for bipolar disorder.

Bipolar disorder (BD) is a complex and currently incurable disease that has attracted a great deal of research. Despite this, neither the pathophysiology of the disorder nor the pharmacology of its treatments is understood.

BD constitutes a far greater public health problem than its occurrence may suggest (approximately 1% of the adult population), owing to the highly destructive nature of manic and depressive episodes. Treating BD poses a significant health cost for a number of reasons. Firstly, patients suffering from BD are prone to attempting suicide, particularly during depressive episodes: documented suicide completion rates are as high as 15% in some studies. Hospitalisation, voluntary or not, is an unfortunate necessity in severe depressive episodes. Secondly, the reckless and destructive behaviour associated with mania can impair the patient's ability to function in a family or employment. Acute mania can put the patients, and those around them, at great risk and is a medical emergency.

Bipolar Disorder (BD):

- An incurable mood disorder that affects approximately 1% of the adult population worldwide with no gender bias
- Diagnosis is defined by the occurrence of at least one manic episode and most patients will experience subsequent episodes that are either manic or depressive
- Episodes can last for months and be separated by years
- BD is divided into a number of subtypes with overlapping symptoms
- It represents a major global health issue with patient suicide rates recorded as high as 15%

From a biological perspective, BD has fascinated researchers from varied fields. The disorder has complex heritability with a polygenic origin that vexes current genomic studies. Also, neurophysiologists are interested in the pathology of a disease that can lead to such opposing behavioural symptoms within the same system. Molecular biologists seek to find the changes in neuronal gene expression that may cause manic or depressive episodes to span months or years while developmental biologists look to embryogenesis for clues. In addition, pharmacologists work to dissect the efficacy of current treatments with an aim to develop new, less toxic medicines. It is the multidisciplinary approach to BD that makes it such a fascinating topic to follow.

Since 1950, lithium carbonate has been the most prescribed treatment for BD:

- Lithium stabilises mood and acts as a prophylaxis for subsequent manic episodes. Also used in treatment of acute mania with ~70% efficacy
- Currently most effective drug in prevention of BD-associated suicide
- Narrow therapeutic window: therapeutic at ~1.0 mM in serum; toxic at ~1.5 mM in serum; lethal at ≥2.5 mM in serum
- Up to 75% of patients treated with lithium experience side effects including weight gain, confusion, hair loss, nausea, thyroid disorder and renal toxicity
- Pharmacology is poorly understood
- Monitoring patients for lithium toxicity is costly for health services

Heritability

Multiple studies have shown robustly that there is a genetic component to the disorder. There is no Mendelian pattern of inheritance of BD, however, and statistical analysis points to polygenic inheritance. Twin studies report that the concordance for BD ranges from 40%-80% in monozygotic twins and from 10%-20% in dizygotic twins. Family and adoption studies have shown that the probability of a sufferer of BD having a child or sibling with the disorder is approximately 10% higher compared with an adopted child or sibling.

Statistical genomics of BD: few rules but many exceptions

Molecular and statistical genetics have refined the search for BD susceptibility genes by two means: genetic linkage studies and association studies. Although these studies have revealed regions of the genome and specific genes associated with BD, a number of obstacles prevent this data from being translated into therapy:

- Studies are hard to reproduce
- Many candidate gene studies use modestly sized samples (typically 100-200 individuals). For complex disorders such as BD this is likely to be insufficient
- Reported levels of statistical relevance are modest
- Chromosome regions of interest are large (typically >20 cM)
- Some regions of interest are implicated in other affective disorders
- Although linking studies have presented several genes as contributors to BD, the potential role of the proteins/RNAs encoded by these genes has yet to be investigated. No susceptibility gene has thus far had its biochemical role in BD fully elucidated

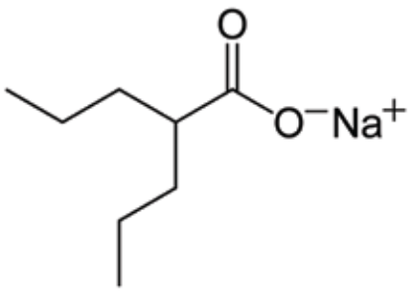
Nevertheless, there is potential in this work and understanding the genetic origin of BD is fundamental to developing new treatments.

Genetic links to other affective disorders: an avenue for new treatments?

One recent advance in the field is the discovery that a number of candidate genes for schizophrenia have also popped up in studies into the genetics of BD, particularly those encoding proteins that mediate neuronal signalling. This implies that the two illnesses lie on a spectrum of affective disorders, rather than existing as discrete illnesses. It is interesting to consider that susceptibility along this spectrum may be governed by overlapping sets of genes. On the back of this data, antipsychotic drugs used in schizophrenia are now being prescribed to treat acute mania in BD with good efficacy, but severe side effects (hair loss and acute nausea) are common.

In addition, Sodium Valproate (VPA), a branched-chain fatty acid that can block sodium ion channels (commonly used to treat epilepsy), also has unexpected efficacy in suppressing mania in BD sufferers. VPA came to the forefront of treatment on the back of studies showing that sodium ion channels can be mutated in BD patients. Despite this success, the therapeutic relevance of blocking sodium ion channels remains unknown.

It is worth pointing out, however,



Sodium Valproate (VPA) is often given to suppress mania.

that links with other diseases have not always proved useful in treating BD. The use of antidepressants in treating unipolar (classical) depression is well documented, but studies over the last 20 years have shown that treating the depressive phase of a BD sufferer with antidepressants can induce a manic phase! The mechanism behind this switch remains elusive.

Neuronal survival: a target for therapy

In addition to genetic analyses, there is growing evidence from biochemical studies that BD is a disease of neuronal activity, with defects in neuronal plasticity and survival. Lithium has been shown to affect neuronal plasticity and survival at multiple levels. By determining the therapeutic mechanisms of lithium, targets for novel drug design can be found.

The changes in gene expression concomitant with chronic lithium treatment have shown that induction of neuroprotective factors may markedly contribute to their therapeutic action. One factor of particular interest is Bcl-2, an anti-apoptotic protein. Bcl-2 has been shown, both *in vitro* and *in vivo*, to inhibit neuronal apoptotic and necrotic cell death induced by a wide range of stimuli. Furthermore, some recent studies have shown that not only can Bcl-2 promote neuron survival, but it can also induce regeneration of axons in the mammalian central nervous system.

The notion that neuroprotection, through regulation of Bcl-2 and other factors, may constitute at least part of the therapeutic effect of lithium has been complemented by recent neuroimaging and post-mortem studies reporting decreased brain volume in patients with BD. Moreover, post-mortem studies have reported reductions in grey matter volume in the prefrontal and temporal cortex in BD patients. Consistent with this, Bcl-2 antibody studies have shown lithium-induced elevation of the neuroprotectant to be most pronounced in the prefrontal cortex.

Though neuroimaging and post-mortem studies are frequently based on relatively small sample sizes, the findings are consistent. Similar reductions in neuron and glial number are associated with unipolar depression. This observation hints at an underlying neuropathology in mood disorders, which could be critical in developing new treatments for BD and other disorders. Characterising the neuropathology of BD may allow future diagnostics through neuroimaging. This could allow more accurate diagnosis and prescription of appropriate treatments.

Conclusion: new treatments dependonbetterunderstanding of BD

Neither the pathophysiology of BD nor the therapeutic pharmacology of its treatments is adequately understood. A number of observations on the genetic and neuropathological basis of the disease have been made, and some studies have provided targets for novel drug design. It is the integration of these single observations into a comprehensive model of the disorder, however, that is critical to develop new treatments for BD. Finally, it is important to appreciate that pharmacology does not represent the entirety of BD treatment. Psychiatric work, combined with education of sufferers and their families, is a vastly important and ever-growing avenue of treatment to avoid the severe effects of this crippling mental disorder.

James Halstead is a second year D.Phil student and is an interested observer of advances in bipolar disorder rather than an expert.

A SHORT HISTORY OF MOLECULAR BIOPHYSICS IN OXFORD (1966 - 1990)

Professor Dame Louise N. Johnson

The Laboratory of Molecular Biophysics (LMB) began in Oxford in 1966 when David Phillips was recruited to an *ad hominem* chair. He brought with him members of the team, Colin Blake and Tony North, from the Royal Institution, London, who together with Phillips had solved the structure of lysozyme, the first enzyme and second protein structure to be solved by X-ray diffraction, and Wynne Browne, a research assistant expert in model building. Two further members were recruited to University positions: Robin Offord who provided expertise in protein chemistry and biochemistry and Andrew Miller who understood fibre diffraction. I joined in 1967, as a Departmental Demonstrator. The lab was housed in Old Physiology, now demolished to make way for the New Biochemistry Building. In 1970 we moved to the newly built Zoology Building on South Parks Road, to spacious quarters on the top floor. Dorothy Hodgkin, who had been most supportive of the move of Phillips to Oxford, had space for her insulin team in the Experimental Psychology building.

The Laboratory had a mechanical and electrical workshop headed by Mike Pickford and John Marsh, respectively. We built much of our own equipment (for example a five-circle diffractometer, an oscillation camera, and a device for cooling crystals to 4°C). When Fred Richards from Yale University came for a Sabbatical in autumn of 1967, having sailed his own boat across the Atlantic, the workshop helped to put his ideas for the Richards Box into action. X-ray diffraction experiments lead to electron density maps. Interpretation of these maps by construction of a molecular model was tremendously laborious in the 1960s. Richards constructed a device using a half silvered mirror that enabled model and map to be visualised simultaneously. The device was used until computer graphics took over in 1979.

The affiliation of Molecular Biophysics with Zoology was unusual. John Pringle, the Head of Department, had a vision of zoology extending from the whole animal to the molecular level. This was exemplified by his own work on the synchronous flight muscle of the bug *Lethocerous cordofanus*. In 1970, Andrew Miller (LMB) and Richard Tregear (Zoology) collaborated to obtain *Lethocerus* muscle fibre X-ray diffraction under forcible oscillation in the presence of calcium and ATP. They showed variation in intensities of the equatorial reflections as the muscle went from relaxed to active state. Intensity changes were

consistent with the movement of the myosin cross-bridges during contraction, with only a small proportion of the cross-bridges attached at any one time. This was an early triumph of time resolved diffraction studies.

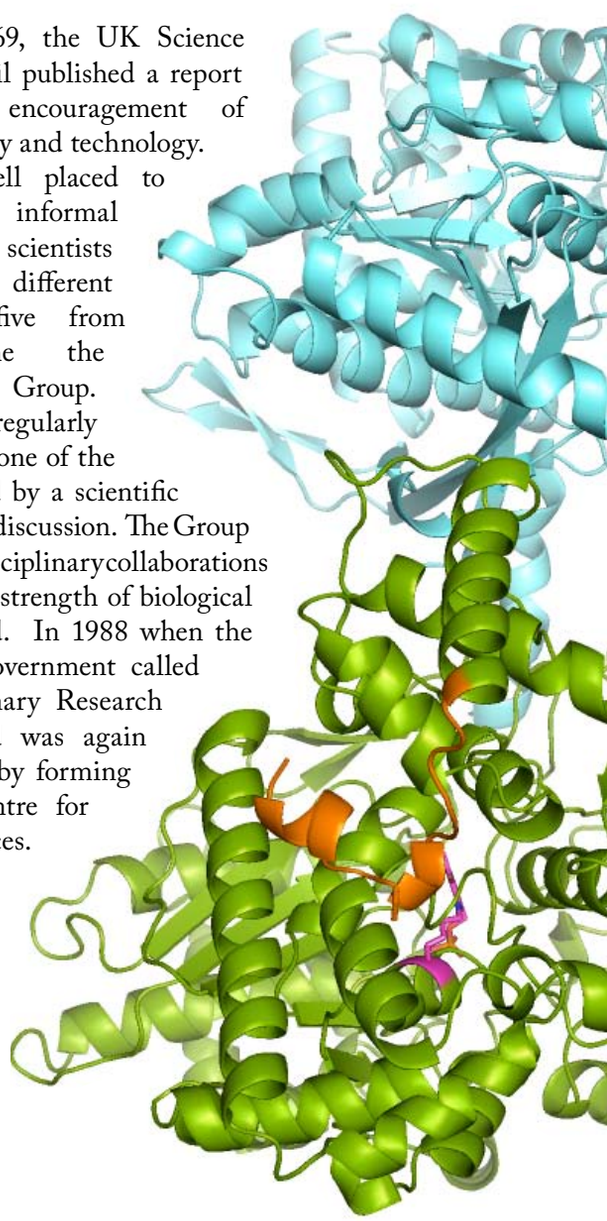
The association with Zoology had many joys but our research collaborations became closer to Biochemistry. In 1985 we moved to the Rex Richards Building, shared with Rodney Porter's MRC Immunochemistry Unit and Iain Campbell's NMR group. The space was adaptable and we continually needed to find more space for wet biochemistry: expression, purification and crystallisation of biological macromolecules. Previously we had been dependent on isolation of proteins from tissue for structural studies but from the 1980s we could use the power of recombinant DNA technology and expression in heterologous hosts to obtain the desired protein in sufficient quantities.

There had been several changes in LMB staff in the intervening years. Several members, including Tony North and Robin Offord, left to take up chairs elsewhere and Andrew Miller became Vice-Chancellor of Stirling University. I was appointed to North's lectureship in 1973 and Tony Rees to Offord's post in 1980. David Stuart was appointed to a New Blood Lectureship in 1985. Garry Taylor was with us from 1982-1989 as Director of Computing. When Taylor arrived we had a PDP 11/70 and when he left we had a Vax cluster with a Vax6210 as the hub and a Convex C210 supercomputer, comparable in power to a Cray 1S, one of the most powerful computers at that time, and three graphics stations – a computing system that was to be continuously revised and enhanced in the years to come. Elspeth Garman was recruited in 1987 with a special remit to mastermind the X-ray diffraction equipment. Following the retirement of Dorothy Hodgkin in 1977 and the move of Guy and Eleanor Dodson to the University of York, Margaret Adams moved to LMB as a Somerville College Fellow. Peter Goodford joined us in 1982, supported by the Wellcome Foundation, and brought expertise in drug design and computational approaches.

As David Phillips' retirement drew close in 1989, the University instigated a review of LMB. Happily, the panel concluded that LMB should continue and the Chair was made a statutory post and named the David Phillips Professor of Molecular Biophysics with endowment from the Edward Abraham Research Fund. In 1990 I was appointed to the Professorship and at that time LMB changed its affiliation from Zoology to Biochemistry with Ed Southern the Head of Department. When Biophysics arrived in Oxford in 1966, some in Biochemistry were sceptical that the new subject had anything to offer Biochemistry. What could the study of an enzyme in the crystalline state tell us about behaviour in the cell? However, the ability of molecular structure to explain biological function dispelled such doubts. By 1990 LMB was contributing substantially to the teaching in Biochemistry and the Structure and Function of Biological Macromolecules became one of the four major subjects of the Part I Final Honours School.

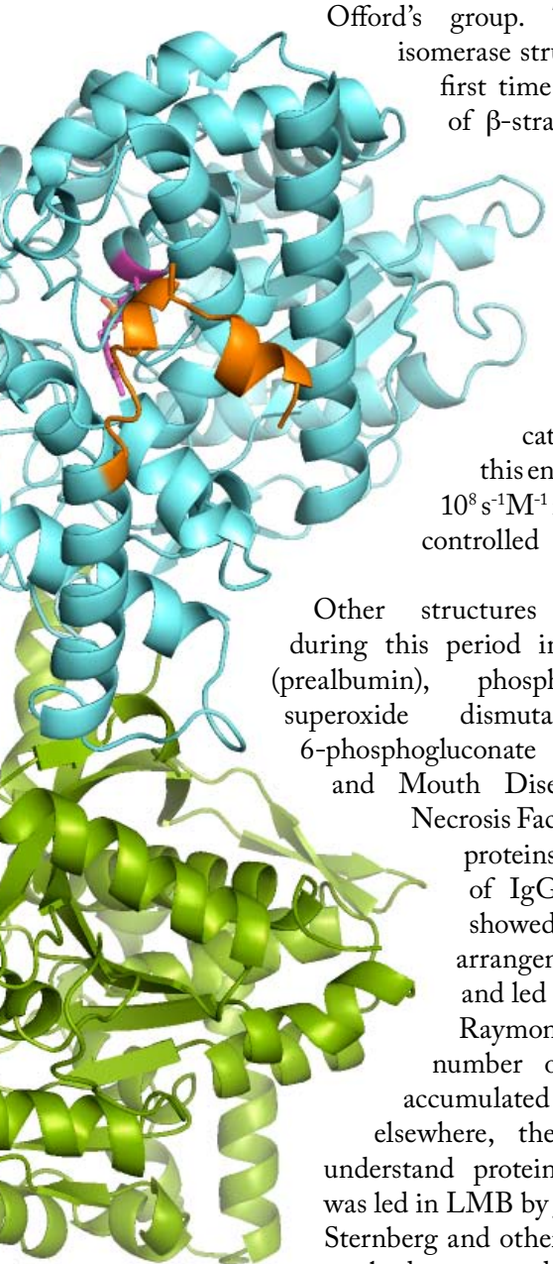
LMB was always a close-knit society but also most keen to attract collaborations. The lab produced its own annual report starting from 1971 and copies were kept up until the last report of 2005, when it was replaced by a web version. David Phillips had been keen to establish a concerted training programme for graduate students, long before such procedures became common elsewhere. From the 1970s graduate students produced a report at the end of their first year and were interviewed by a panel of staff. They were interviewed again at the end of their third year. They gave seminars in their first year and in their third year. For many years, LMB was the main training centre for structural biology and as the subject expanded in other Universities, LMB graduates filled many of the new positions.

In February 1969, the UK Science Research Council published a report recommending encouragement of enzyme chemistry and technology. Oxford was well placed to respond. An informal grouping of 22 scientists from eight different Departments (five from LMB) became the Oxford Enzyme Group. The group met regularly with a dinner at one of the colleges followed by a scientific presentation and discussion. The Group promoted interdisciplinary collaborations and it led to the strength of biological NMR in Oxford. In 1988 when the Conservative Government called for Interdisciplinary Research Centres, Oxford was again able to respond by forming the Oxford Centre for Molecular Sciences.

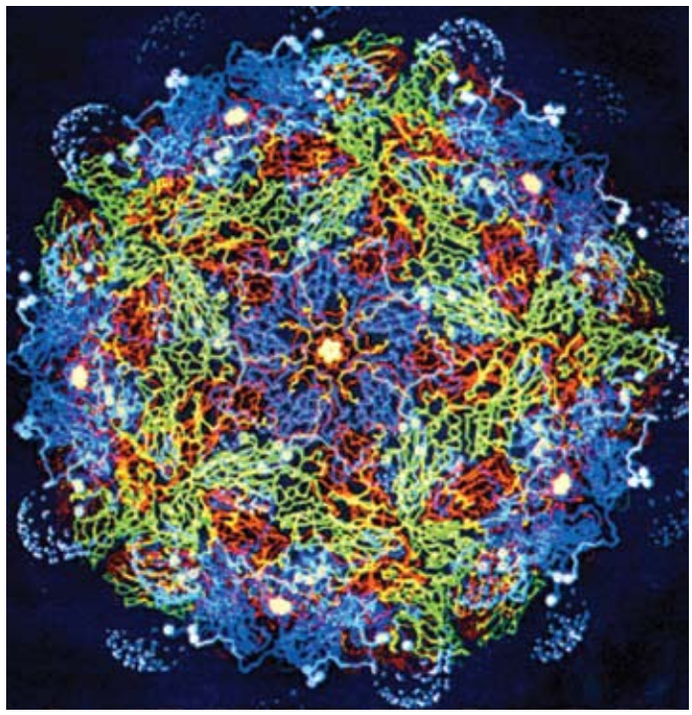


GPb: glycogen phosphorylase b (one subunit cyan other subunit green, N-terminal region orange).

The study on the glycolytic enzyme triosephosphate isomerase was one of the early collaborative projects of the Oxford Enzyme Group. Encouraged by Phillips, I had started work on this enzyme in 1967 with crystals grown by Stephen Waley from the Ophthalmology Department. Our X-ray sources were so weak that exposures to record even a 2D diffraction pattern took a long time. The first successful X-ray exposure was with a precession camera with photographic film and it took 50 hours (over a weekend). During that time I walked with a friend from Harwell to Avebury along the Ridgeway. Imagine my joy when at the end of the walk I came into the lab to develop a most beautiful photo that showed the diffraction pattern was good enough for structure determination. The structure was eventually solved in 1975 by David Phillips and his team using the amino acid sequence determined by Robin Offord's group. The triosephosphate isomerase structure showed for the first time the eight-fold repeat of β-strand and α-helices, in what has become the most frequently observed protein fold. The chemical studies by Jeremy Knowles and Stephen Waley led to a deep understanding of the catalytic mechanism of this enzyme, whose $k_{cat}/K_M \sim 10^8\ s^{-1}M^{-1}$ is close to the diffusion controlled association rate.



Other structures solved in LMB during this period included transthyretin (prealbumin), phosphoglycerate kinase, superoxide dismutase, α-lactalbumin, 6-phosphogluconate dehydrogenase, Foot and Mouth Disease Virus, Tumour Necrosis Factor, blood coagulation proteins and the Fc fragment of IgG. The last structure showed for the first time the arrangement of carbohydrate and led to collaborations with Raymond Dwek. As the number of known structures accumulated from LMB and elsewhere, there was a drive to understand protein folding, work that was led in LMB by Janet Thornton, Mike Sternberg and others, and computational methods were developed. An early contribution was that of Keith Wilson and Simon French, who used Bayesian statistics to teach us how we should evaluate negative intensities, a problem that had troubled crystallographers since the 1940s.



Protein structures from LMB: FMDV, Foot and Mouth Disease Virus complete icosahedron.

To end on a personal note, I began work with glycogen phosphorylase in 1971 and this project occupied most of my research effort for the next twenty years. At that time phosphorylase was the largest single chain protein to be studied by crystallography. It was a fascinating problem for structural biology because the enzyme exhibited both non-covalent regulatory mechanisms and control by phosphorylation. We succeeded in co-crystallising the enzyme in the less active state (T state). The new UK synchrotron at Daresbury opened in 1981 and we were among the first users. Using the experimental station 7.2 built by John Helliwell (who had completed his D.Phil with Margaret Adams), and with the leadership of Keith Wilson from my group, we were able to carry out structure determination and ligand binding studies. These studies led to the high-resolution structure with Ravi Acharya and David Stuart driving the work forward and Mark Sansom contributing to the refinement. Later Janos Hadju started time resolved studies with Laue diffraction, allowing us to follow catalysis in the crystal. For many years the major problem, that of the phosphorylase structure in its activated phosphorylated state, eluded us until David Barford solved the problem in 1989.

In this short account I have not been able to mention many who contributed to LMB in this period, nor have I been able to do justice to all the structural problems addressed or the instrumental and computing developments. I hope the history of the second phase of LMB (1990-2007) will be written in the not too distant future and the third phase, yet to come, will be as full of joy, fun, excitement and reward as these years.

5' WITH...

Professor Iain Campbell

Iain Campbell's research group studies the structure and dynamics of integrin adhesion complexes that form during cell migration. He is a Fellow of St John's College.

When did you realise that you wanted to be a scientist?

I spent my childhood in a small Scottish village with lots of exposure to the natural world. At Perth Academy, my grammar school after 11+, I found that I had more aptitude for science and maths than other subjects. At school in the 1950s, in the aftermath of WWII, there was a general feeling that physics had great potential for both good (technology development) and bad (atom bombs). My natural optimism led me to believe in the good so I chose to study physics at University. I enjoyed that and stayed on at St Andrews to do a PhD in solid state physics but did not really feel that that was what I wanted to do. My move towards biochemistry in later years did feel like the right thing to do.

If you were not a biochemist, you would be...

As a boy I used to imagine myself as a cold-war spy but I could perhaps also think of myself as the local GP in a small Scottish town.

Your favourite book...

My book reading is eclectic, often done while travelling to meetings. I am currently fond of Scottish novelists, e.g. Iain Banks' The Crow Road (better as a book than a TV series). I also like the OUP VSIs (very short introductions) which give brief readable accounts of a wide variety of topics (philosophy, consciousness, history of art etc.).

If you are not in the lab you are...

At scientific meetings (peer review, conferences) or spending time (not nearly enough) with my wife (of nearly 43 years), three children and five grandchildren.

Worst disaster in the lab?

Fortunately no real disasters, although we have, of course, had centrifuge accidents and superconducting magnet 'quenches' where large amounts of liquid helium boiled off in a very short time from our large NMR magnets.

What has been the most important moment of your career so far?

I am not sure I want to pick out one moment. My career has been an accumulation of rewarding moments: getting

an experimental result that gives new insight into how something works; seeing the results in published form; giving lectures at meetings and sharing ideas with colleagues. These make everything worthwhile, a great pleasure and a privilege.
While perhaps not 'the most important moment of my career' I am very conscious that I 'retired' this year. I was very touched by the kindness shown by numerous ex-students who came to a small celebration at St John's last September. This 'retirement' event was an important moment for me, one that enhanced my awareness and appreciation of such a loyal and talented team of people around me.

In your view, what is the importance of luck in research?

I have already alluded to luck and good fortune several times. I was hired by the Oxford Enzyme Group in 1971 to set up a nuclear magnetic resonance (NMR) laboratory in the Department of Biochemistry. We had enough money and resources to construct the best instrument in the world at that time. Up to then, NMR had played no significant part in biochemistry. The new generation of instruments that began in the early 1970s gave us the ability to study macromolecules as well as small molecules in cells and tissues in completely new ways. These were exciting times for NMR and I was in the right place at the right time to be involved in the new developments.

"[EGF] was the first NMR protein structure to be done in this country"

Any memorable findings?

One highlight has to be the determination of the structure of epidermal growth factor that we published in 1987. This structure also gave insight into the role of EGF domains in a wide variety of other proteins and it was the first NMR protein structure to be done in this country.

Describe your personality in four words.

Focussed; open minded; driven but cautious.

One human trait you hate.

I hope I am pretty tolerant of most human traits. We all have a distribution of them; we need to try to skew the distribution towards the more attractive.

Favourite vacation spot.

I think I prefer new vacation spots each time rather than repetition. Memorable vacations include camping in Les Gorges du Verdon with young children.

Best advice you ever received.

Strangely, I do not recall any very memorable advice, although my various mentors including Rex Richards, Bob Williams and Walter Bodmer were always encouraging and helpful. Maybe this lack of recall shows me to be someone who makes up his own mind about the way to proceed rather then being too much influenced by others.

What has been your biggest mistake or regret?

I have no serious regrets although I should have been more sociable and more intimately involved in family life. It is easy to get obsessive about science and close relatives around you can suffer.

Favourite classical experiment?

As someone who has made a career out of NMR, especially in my earlier research years, I should mention the Nobel prize-winning (Physics, 1952) efforts of Felix Bloch and Ed Purcell in the 1940s which led to the first observation of NMR signals.

How do you imagine biochemistry research will change in the next twenty years?

It has already changed beyond recognition during my life time as a scientist. When I started in Biochemistry in 1971 only a handful of protein structures were known and hardly any sequence information was available. Now we know over 50,000 structures, as well as the entire genome sequences of numerous organisms. Our future task is to try to understand how large numbers of 'dead' molecules assemble to form a 'living' cell. We now have powerful tools that allow us to observe events in the scale where life emerges (~0.1 nm to 10 μm). To understand the molecular basis of life we need to study the structure and dynamics of many intricate interaction networks. To determine how molecules are assembled and regulated in the living cell is clearly a major challenge but it is an exciting and profound challenge; one that will keep us busy for a long time to come.

SCIENCE AT ITS CROSSROADS

"I CHOSE THE PATH LESS TRAVELLED"

Marvin Lee is a third year D.Phil student working in Dr Terry Butters' laboratory at the Glycobiology Institute in the Department of Biochemistry. He tells us about his experiences on the Scripps-Oxford research programme.

With more than 1,000,000 square feet of space overlooking the Pacific Ocean in La Jolla, The Scripps Research Institute (TSRI) is more than just a playground for both established and budding scientists from all over the world. It is also an ideal spot for avid surfers and beach goers. One of the many incentives of being part of the institute is the opportunity to engage in a plethora of sports and activities outside of the laboratories. If you're lucky, you might actually spot Tiger Woods swinging his golf club on the putting green the next time you stick your head out of the window from your workbench! If the science is letting you down, never mind, just zip outside and you are immediately greeted by warm sunshine (a rare treat in Oxford). What more can one ask for?

Marvin Lee

I have made the trip across the Atlantic from Oxford four times now and each visit proves to be an eye-opener. Talk to any group leaders or students about their scientific brainchild and their eyes immediately sparkle with ardent fervour. TSRI is undoubtedly an enchanting mixing vessel where the brightest scientific talents from all corners of the globe congregate to foster world-class research.

The annual graduate symposium held at the Bahia Resort on 11 September 2009 was attended by current graduate students from the various departments across TSRI, including counterparts from Scripps Florida and students on the Skaggs-Oxford Scholarship Programme like me. Each year, the day-long symposium takes place at the ballroom on the top floor of the resort, overlooking the inviting blue waters of Mission Bay. Light breakfast is served before jittery students take the stage to give their presentations in front of a somewhat intimidating crowd of established scientists. There is a comfortable mix of biology and chemistry talks, interspersed with two short poster sessions where the researchers casually bounce scientific ideas off one another over coffee and biscuits – a fantastic networking opportunity.

This year it was a great privilege to hear about the highly acclaimed study led by Damien Ekiert that had been published in *Science* in April 2009. This research led to the discovery of the cross-protective CR6261 antibody against the influenza virus, marking the first step towards the development of a universal flu vaccine. Supervised by Professor Ian Wilson, the group highlighted the interaction of several monoclonal antibodies against the influenza haemagglutinin, based on structural and mechanistic data. There were many other riveting presentations, ranging from stem cell research and immunology to total syntheses and quorum sensing. The distinguished faculty lecturer presentation was given by Professor KC Nicolaou. He referred to chemistry as a central science, linking the subject to a diversified array of topics such as medicine, material science and biology.

The Skaggs-Oxford Scholarship Programme is an invaluable opportunity for me to experience the different dynamics in erudition in Britain and the United States. Appreciation of these differences will serve as an important communication tool in bridging international research collaborations and in opening up new knowledge frontiers during the fulfilment of my scholarship commitment in Singapore. My home country has been striving to build the biomedical sciences industry from scratch into the fourth pillar of its manufacturing sector for almost a decade. Collaborating with and emulating the established players in the market such as Britain and the US is very important in this development.

This prestigious programme gave me the flexibility to begin my research career either at Oxford University or TSRI, and I chose to do the former. Having spent slightly over two years working on a compelling project on viral protein folding with Dr Terry Butters in Oxford, I will be relocating to the newly inaugurated Scripps research campus in Florida early in 2010, engaging a brand new project, ploughing through a different compilation of research papers and addressing an unfamiliar audience during lab meetings. The transition will be a challenge, but it will definitely be an adventure.

For more information about the Oxford-Scripps Programme visit http://www.scripps.edu/phd/skoxford/

OXFORD

SCRIPPS

Science and the Web

Sonya Hanson

Five years ago, when graduate student Alice Pawley started her blog (http://scienceblogs.com/sciencewoman/) about being a woman in science, finding a community to share her experiences with was not easy. It took weeks, she wrote, to find even one blogger in a similar situation. Now she is an assistant professor and last December she posted that she would soon stop blogging, bidding farewell to a now large blogging community that continues to expand. While the number of people who have taken their personal and professional lives to the internet is staggering, what is more relevant is the growing number of tools we have to organise this information for ourselves, maximising the information we can gather from the internet while minimising the time we spend on it. Although it may be hard for some to admit, it seems that in the last few years the internet has become increasingly useful.

As young scholars of biochemistry, we are in a privileged position to take advantage of these tools, and to incorporate them into our routine. Our peer-to-peer networks are becoming increasingly web-based, top tier scientists share their interests openly via easily accessible sites and high impact journals are beginning to grasp the power of new technologies. This means that having even a loose handle on these newer methods of communication can make all the difference.

The fact is we are now much more likely to spend our time browsing the internet than we are a library. Unlike a library, however, we are each charged with the task of designing our own personalised Dewey Decimal system to organise our resources. Some will keep it simple and stick to getting e-mails or RSS feeds of a PubMed search, an almost effortless way to be kept up-to-date on topics of interest. Others might go a little further and listen to *Science* or *Nature's* weekly podcasts. Those who are already acquainted with Twitter may feel most comfortable following a few of their favorite scientists, @Naturenews or @AdamRutherford, a *Nature* editor who gave a talk in November 2009 to the Oxford Biological Society. Those with a penchant for blogging, and perhaps a little too much time on their hands, may start delving into the enormous scientific blogosphere from which websites such as http://scienceblogs.com/ and http://www.postgenomic.com/ try to provide highlights. Others might try to collect all this information to view at a glance on their Google Reader and iGoogle homepage. However you go about it, it now seems like almost everyone is finding a preferred way to organise their internet resources.

Of the many questions we could ask of these new tools and their application to our lives, one stands above the rest: is all this really going to increase our productivity and make us better scientists? A particularly compelling story I found was of the blog of Fields Medal recipient Professor Timothy Gower of Cambridge University. Through his blog, a collaborative community was formed that within six weeks came up with a new proof to a long-standing mathematical problem. Having been fruitful in their experiment to bring expertise together through the internet, they are now trying their luck with a new format: a Wiki. While it is still unclear if biomedical science can benefit in the same ways as the mathematical community, there is certainly scientific potential in this new connectivity, however you choose to harness it.

Sonya Hanson is a first year D.Phil student in Professor Mark Sansom's lab in the Department of Biochemistry. She is currently working at the NIH in the US with co-supervisor Dr Kenton Swartz.

Are you a member of the Biochemistry Department?

Do you have a news story that people might be interested to read on the Biochemistry Department's website? This could be scientific news, for example, an important paper about to come out, a substantial grant awarded, or other research news. Or it could be more personal, for example, if you have been awarded a prize, or if you have a story which has some connection with your work or the Biochemistry Department which might be of more general interest. If you have some news, please do let me know about it.

With thanks, Jane Itzhaki (Department of Biochemistry web news writer)
jane@itzhaki.wanadoo.co.uk

SNAPSHOT

We are happy to announce that this issue's winner of the *Snapshot* research image competition is Dr Fernando Martinez-Estrada from the Sir William Dunn School of Pathology. Dr Martinez-Estrada is a postdoctoral researcher in Dr David Greaves' laboratory who submitted a stunning image of multinucleated giant cell (MGC) formation (featured on the front cover of this issue). As the winner of *Snapshot* Hilary 2010, he has won £50 of books from Oxford University Press, a bottle of champagne and a copy of "The Oxford Biochemistry Department 1920 - 2006" by Dr Margery Ord. Again, we were very impressed with the quality of the images submitted this term and are grateful to all those who entered, so please keep them coming!

Cell to cell fusion is a ubiquitous event that occurs in a wide range of biological processes. Well known examples include both sperm-oocyte and myoblast-myoblast fusion. In the immune system, macrophages and their precursors also undergo fusion resulting in the formation of MGCs. These cells are present in chronic inflammatory reactions, granulomatas, tumours and also participate in the foreign body reaction. Despite their well characterised presence, little is known about the properties of these cells or the mechanism of fusion itself. In late 2006, Dr Martinez-Estrada joined the laboratory of Prof. Siamon Gordon to study different aspects of human MGC formation and function and he now continues this work with Dr Greaves.

The cells photographed correspond to a novel model of human macrophage-macrophage fusion developed by Dr Martinez-Estrada. The actual fusion process in this model takes 24 hours as opposed to conventional models that take 10 to 15 days. The figure shows an immunofluorescence microscopy image of human MGCs. Human monocytes were cultured for three days prior to induction of fusion with interleukin 4. This level of fusion is achieved within 24 hours post fusion-induction. Actin (Red) was visualized by staining with Phalloidin conjugated to Alexa-633. Beta-tubulin (Green) was detected with a monoclonal antibody conjugated to Alexa-488 and the nuclei were stained with DAPI.

Further Reading:

Helming L, Tomasello E, Kyriakides TR, Martinez FO, Takai T, Gordon S, Vivier E. (2008) Essential role of DAP12 signaling in macrophage programming into a fusion-competent state. *Sci Signal.* Oct 28;1(43):ra11.

Helming L, Gordon S. (2009) Molecular mediators of macrophage fusion. *Trends Cell Biol.* Oct;19(10):514-22.

Snapshot Trinity 2010: 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 the Trinity 2010 *Phenotype*.

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 Friday 5 March 2010.

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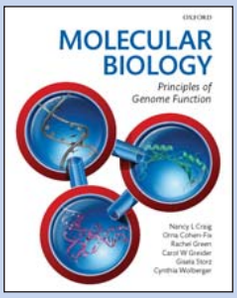
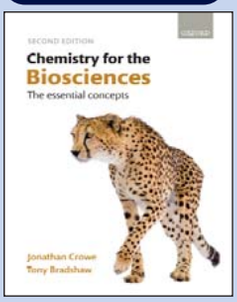


Molecular Biology
Principles of Genome Function

Nancy Craig, **Orna Cohen-Fix**, **Rachel Green, Carol Greider, Gisela Storz**, and **Cynthia Wolberger**

A new approach to molecular biology for the twenty first century

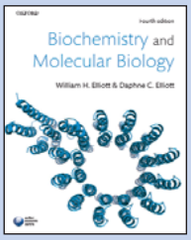
new edition

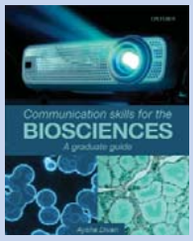


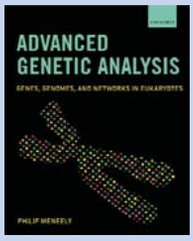
Chemistry for the Biosciences
The essential concepts | Second Edition

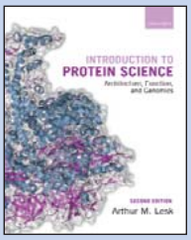
Jonathan Crowe and **Tony Bradshaw**

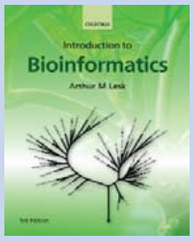
Focuses on the key chemical concepts which students of the biosciences need to understand











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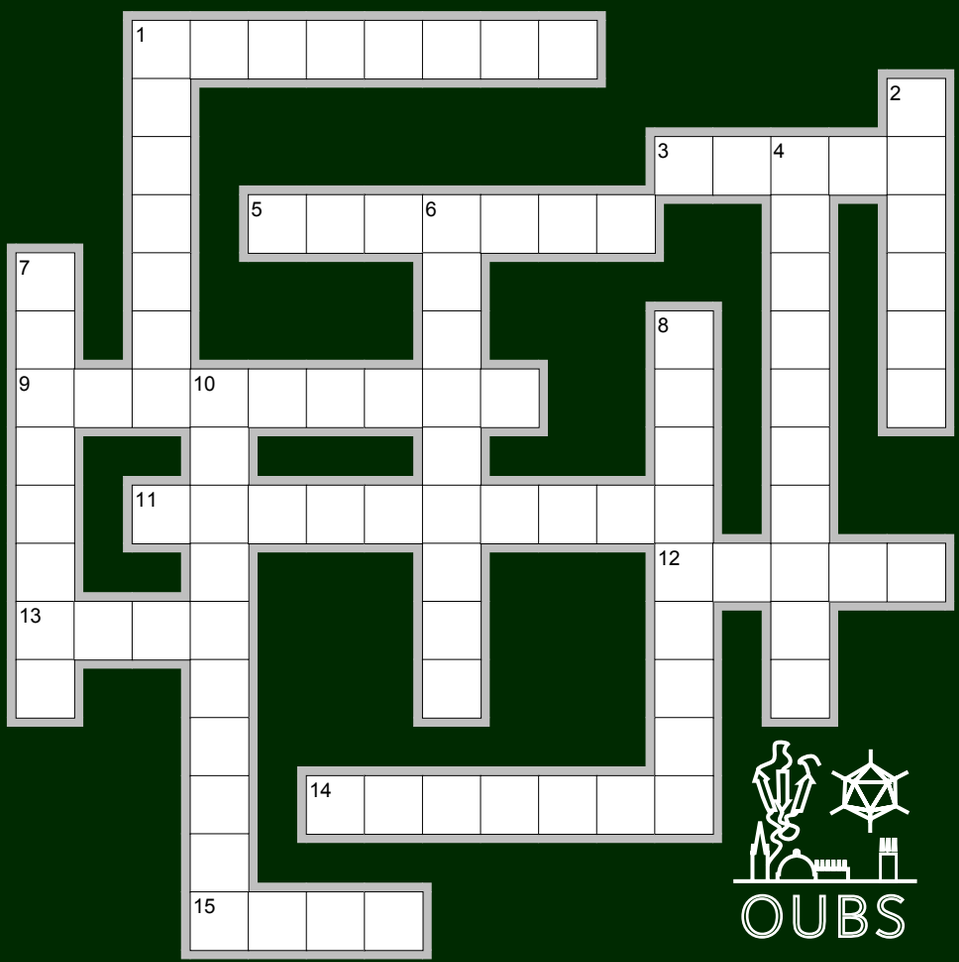
You can e-mail us the answers (oubs@bioch.ox.ac.uk) or leave a paper copy in a sealed envelope in the OUBS pigeon-hole at the New Biochemistry reception.

Congratulations to Shee Chien Yong from the Biochemistry Department, who won the Michaelmas '09 crossword competition.



Across

1. Controversial results were presented in 2009 about the development of a vaccine against HIV. Where did the clinical trial take place?
3. American president who lifted the ban on federal funding for research on stem cells in 2009.
5. Scientist who also proposed a mechanism for the evolution of species; the 200th anniversary of the publication of his book was celebrated in 2009.
9. Scientist who won the Nobel Prize in Physiology or Medicine for her discovery of telomeres and telomerase.
11. Early-life stress was shown to cause what type of effects in mice?
12. South Korean scientist convicted in 2009 after his research on stem cells was found to be fraudulent in 2006.
13. Location of a famous landing that had its 40th anniversary in 2009.
14. Last year we celebrated the 40th anniversary of the first message sent between computers through a network, a project that would eventually lead to the internet. What was the name of this project?
15. Scientific adviser to Home Secretary Alan Johnson who was sacked in 2009 for publicly criticising the government's drug policies.

Down

1. The Ig Nobel Prize in Chemistry was awarded to scientists at Universidad Nacional Autónoma de México, for creating diamonds from which alcoholic beverage?
2. Famous particle collider that was under repair for most of last year.
4. Type of anti-virals to which swine flu is resistant.
6. 2009 was the international year of which area of science?
7. The Nobel Prize in Chemistry was awarded in 2009 for the work on the structure and function of which molecule?
8. American biochemist who died in May 2009. His discoveries concerning nitric oxide and the cardiovascular system earned him the Nobel Prize in 1998.
10. Location of the 2009 United Nations Climate Change Conference.